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Feasibility Study of a Novel Diet-Based Intervention for Prostate Cancer

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14. ABSTRACT My goal is to develop a practical, diet-based intervention for prostate cancer. During the award period, I implemented a randomized clinical trial of a novel dietary intervention for prostate cancer that promotes vegetable intake among prostate cancer patients on active surveillance. I successfully expanded the protocol described in the original Statement of Work from a randomized clinical trial involving 2 study sites and 200 patients to a national trial involving at least 45 study sites and 464 patients. As of September 24, 2013, the study had achieved 60% of its targeted accrual and was enrolling an average of 10 patients per month. To perform the expanded trial, I helped secure almost \$3 million in additional funding. I presented a study abstract at a national meeting, wrote a manuscript that is pending submission to a peer-reviewed journal, and completed the first planned interim analysis (the results of which exceeded expectations). This award has greatly increased my national exposure, led directly to leadership positions in a NCI-sponsored clinical research network, and honed my clinical research skills. This study is the first national, Phase III trial designed to test a diet-based intervention for prostate cancer and the first non-industry sponsored trial designed to test an intervention of any kind in prostate cancer patients on active surveillance. When completed, it has the potential to substantially inform treatment paradigms for prostate cancer.				
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I. Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous cancer and the second leading cause of cancer death among U.S. men. In addition, accumulating data suggest that widespread population screening has prompted the indiscriminate, inappropriately aggressive treatment of early stage prostate cancers with surgery or radiation, resulting in large numbers of prostate cancer survivors suffering from chronic, burdensome side effects that significantly decrease quality of life. These observations pose great challenges to the public health and call for the development of innovative approaches to prostate cancer prevention and treatment.

One potential novel approach is dietary modification. Epidemiological and pre-clinical studies suggest that specific alterations in nutritional intake may protect against prostate cancer initiation and progression. However, despite widespread public interest in this topic, there are very few clinical studies investigating the potential benefits of diet-based interventions for prostate cancer.

My colleagues and I successfully developed and pilot tested a telephone-based dietary intervention for prostate cancer patients based on well-established principles of social cognitive theory.^{1,2} This relatively straightforward, low-cost intervention—which utilizes behavior modification to increase vegetable intake and decrease fat intake—is the first to utilize diet as a form of primary clinical therapy for prostate cancer. Due to its practicality, simplicity, and proven benefits to cardiovascular and overall health, this intervention would be widely applicable. Use in an active surveillance (“watchful waiting”) population may potentially spare thousands of patients each year from the considerable side effects of surgery and radiation.

I hypothesize that a vegetable-intense diet will decrease disease progression and improve quality of life in men with prostate cancer. My goal is to develop a practical, diet-based intervention for prostate cancer. I have implemented a national, randomized clinical trial of a novel dietary intervention—the Men’s Eating and Living (MEAL) study—that utilizes a central, telephone-based counseling program to promote vegetable intake among prostate cancer patients who are being treated with active surveillance.

II. Body

Research Accomplishments

1) Development and implementation of a national randomized clinical trial based on the original Statement of Work

Our preliminary data, obtained in a pilot trial, established the feasibility of utilizing a telephone-based intervention to robustly alter diet in prostate cancer patients^{1,2} and provided the framework for the design of the two-site, randomized clinical trial (RCT) outlined in the original Statement of Work (SOW). A National Cancer Institute (NCI)-funded cooperative study group, Cancer and Leukemia Group B (CALGB), funded the pilot trial.

As a result of both the successful pilot study and the obtainment of this award, CALGB leadership expressed an interest in fostering further investigations of prostate cancer and diet. They invited me to expand the scope of the original SOW and to develop a multi-center, national RCT utilizing the CALGB infrastructure.

The development of the national RCT required both extensive preparation of a new study protocol and the obtainment of additional extramural funding. To accomplish these tasks, I substantially expanded my participation in the CALGB organizational structure: I joined the CALGB Genitourinary Surgery, Genitourinary, and Prevention Committees, and attended meetings in Chicago on a regular basis. Through these meetings—as well as through e-mail correspondence and conference calls—I conferred with other clinician scientists in the CALGB network to design a larger RCT.

During year 1 of the support period, I revised the study aims, reworked the power calculations to include 464 patients, and addressed the practical considerations related to the performance of a multi-center RCT. I co-wrote and submitted a revised study proposal—based extensively on the study plan outlined in the original SOW—as a RO1 application to the NCI to fund the expanded RCT. The intervention and the primary outcomes of the expanded RCT are identical to those listed in the original SOW. I also wrote a grant that was awarded \$10,000 from the Hope for a Cure Foundation. I pursued these activities with the approval of my Army Contracting Officer Representative. Notably, the support of this award was essential to the completion of these endeavors. I reported the details of these activities in my annual report submitted in 2009.

By the end of year 1, after two revisions, the NCI awarded the study proposal \$2.5 million to perform the expanded RCT (1 R01 CA132951-01A1). Dr. James Marshall of Roswell Park is listed as the Principal Investigator. I am the Protocol Chair of the Study. As Protocol Chair, I share the ultimate responsibility for the orderly and scientific conduct of all research activities associated with the trial.

During year 2, I worked on obtaining human subjects research approval from the Department of Defense (DoD), secured formal approval to run the study from CALGB, completed—after five rounds of revisions by CALGB leadership and personnel—the detailed study protocol (**Appendix 1**), submitted the protocol to the NCI for formal approval in order to open the study for enrollment, submitted a study abstract that was accepted to the DoD Innovative Minds in Prostate Cancer Conference (**Appendix 2**), and co-wrote an additional grant to support the study that was awarded \$300,000 by the Prostate Cancer Foundation. I reported the details of these activities in my annual report submitted in 2010.

During year 3, I secured final approval for the study from the NCI, obtained IRB regulatory approval at each of my home institutions for which I am the site PI—the University of California San Diego (UCSD) and the San Diego Veterans Administration Hospital (San Diego VA Hospital)—for the study, and oversaw the enrollment of the first patient at UCSD. I also obtained endorsement for the study from the Southwest Oncology Group (SWOG). The SWOG is, like CALGB, a NCI-sponsored clinical trials cooperative group. SWOG coordinates hundreds of clinical trials sites nationwide. I presented the study to the SWOG urological trials leadership; they in turn issued an official endorsement of my study that substantially increased the number of potential sites nationwide. I reported the details of these activities in my annual report submitted in 2011.

During year 4, I continued to direct the accrual of patients nationally, successfully opened the study at the San Diego VA Hospital, oversaw several formal revisions to the study protocol (including but not limited to clarification of the inclusion/exclusion criteria, addition of an exclusion criterion for patients taking a class of medications known as 5-alpha reductase inhibitors, and revision of the follow-up prostate biopsy protocol), and discussed the study during a presentation to over 100 clinical research associates and research nurses titled “The Men’s Eating and Living (MEAL) Study (CALGB 70807): A Randomized Trial of Dietary Intervention in Men on Active Surveillance for Prostate Cancer”). In addition, I gave an invited presentation to the SWOG leadership team titled, “The Men’s Eating and Living (MEAL) Study (CALGB 70807): An Update.” As part of this presentation, I answered questions regarding the aims and conduct of the study, and I participated in a discussion of the future of clinical trials in prostate cancer patients on active surveillance programs. I reported the details of these activities in my annual report submitted in 2012.

During year 5, I continued to guide the study protocol through regular contact with Alliance personnel and collaborators at participating sites, oversaw the accrual of patients nationally and at my two local sites (UCSD and San Diego VA Hospital), successfully completed the first planned interim analysis of baseline prostate biopsy data, wrote a manuscript for submission to a peer-reviewed journal, co-wrote and implemented additional revisions to the study protocol, and expanded my activities in CALGB (known now as the Alliance for Clinical Trials in Oncology) to include additional leadership roles. The details of these activities appear in this report.

2) National enrollment

Through phone calls, e-mail correspondence, presentations, and face-to-face meetings, I have personally overseen the expansion of the study and recruited additional sites to participate since it opened during award year 3. Enrollment has gained momentum and has now achieved a steady pace of approximately 10 patients per month. By the end of year 3, when the study first opened, 28 patients had been randomized to study. By the end of year 4, 143 patients had been randomized to study.

As of September 24, 2013, 269 of the targeted 464 patients (58%) had been randomized to study, with 45 different sites across the nation actively accruing.

3) Study enrollment at the Moores UCSD Comprehensive Cancer Center

At the Moores UCSD Comprehensive Cancer Center, at which I am an attending physician who regularly participates in the clinical care of prostate cancer patients, I oversaw identification, screening, and recruitment of patients.

As of September 24, 2013, we had accrued 30 patients to study, making UCSD one of the top two accruing sites nationally (tied for first).

4) Study enrollment at the San Diego VA Hospital

At the San Diego VA Hospital, at which I am an attending physician who regularly participates in the clinical care of prostate cancer patients, I oversaw identification, screening, and recruitment of patients.

As of September 24, 2013, we had accrued 12 patients to study.

5) Successful response to ongoing administrative review of UC San Diego, and San Diego VA Hospital human subjects protection protocols

During years 3 through 5, I successfully responded annual IRB reviews of the study at UC San Diego and the San Diego VA Hospital.

6) Successful completion of the first planned interim analysis of baseline prostate biopsy data.

The study protocol stipulated that the baseline prostate tissue samples of the first 50 patients enrolled to study would undergo central pathology review and analysis at the Alliance for Clinical Trials in Oncology (formerly CALGB) Biostatistical Center to confirm eligibility. The expectation was that no more than 10% of the patients would become ineligible for the study based on central pathology review: a result indicating

>10% of patients ineligible would necessitate recalculation of the study sample size. The results of this analysis, completed in October 2012 (award year 5), exceeded expectations: only 1 of 50 patients (2%) became ineligible for the study after central review.

7) Oversight of the national study protocol

Once the study opened during award year 3, I continued to guide the study protocol through regular contact with Alliance personnel and collaborators at participating sites. I oversaw several formal revisions to the study protocol, including but not limited to additional clarifications of the inclusion and exclusion criteria.

Problem Areas

Although there are no current problems impeding performance, and the RCT is accruing patients at a steady pace, the RCT will finish after the completion of the award period.

The original DoD award timeline estimated that the RCT would open to accrual in March 2009 and be completed by April of 2014. With the extra time required to secure additional funding from the NCI and the PCF, as well as guide the expanded protocol through numerous national review processes and regulatory approval steps, the trial will finish approximately 3 years behind the original projected completion date—at the current accrual rate, by May of 2017.

It is worth noting that the initial delays in opening the trial resulted directly from the unexpected—yet highly fortunate—opportunity that arose for expanding the study from its original two-site pilot design to a national RCT now involving 45 different sites and hundreds of additional patients.

III. Key Research Accomplishments

- Successful redesign of the study as a national RCT (**Appendix 1**).
- Successful obtainment of 3 additional grants for the study.
- Successful accrual and randomization of patients.
 - A total of 269 patients randomized to study as of September 24, 2013, 58% of the targeted total.
- Recruitment of 30 patients to study as of September 24, 2013 at the UCSD Moores Cancer Center.
- Recruitment of 12 patients to study as of September 24, 2013 at the San Diego VA.
- Successful response to ongoing administrative review of UC San Diego and San Diego VA Hospital human subjects protection protocols.
- Presentation of a study abstract at a national meeting.
- Completion of the first planned interim analysis of baseline prostate biopsy data, the results of which exceeded expectations.
- Completion of a manuscript describing the study which is being submitted to the peer-reviewed journal *Contemporary Clinical Trials*.
- Continued participation in Alliance for Clinical Trials in Oncology (known formerly as Cancer and Leukemia Group B) activities, including conference calls, meetings in Chicago to update Alliance leadership on the status of the trial, and formal presentations to Alliance personnel.
- Successful continued oversight of the study protocol, including but not limited to:
 - Regular correspondence with Alliance personnel and collaborators at participating sites across the U.S.
 - Design and implementation of several protocol amendments, including but not limited to additional clarifications of the inclusion and exclusion criteria.
 - Resolution of numerous questions and practical issues posed by study coordinators and collaborators at participating sites
- Recruitment of additional sites, with 45 sites currently participating across the U.S.

IV. Reportable Outcomes

- Abstracts and Presentations

- a. Abstract: **Parsons JK**, Pierce JP, and Marshall J. The Men's Eating and Living (MEAL) Study: a randomized trial of diet to alter disease progression in prostate cancer patients on active surveillance. Presented at the Department of Defense Innovative Minds in Prostate Cancer Meeting; March 2011; Orlando, FL (**Appendix 2**)
- b. **Parsons JK**, Pierce JP, Mohler J, Paskett E, Jung S, Humphrey P, Newman V, Taylor JR, Barbier L, CL Rock and Marshall J. A randomized trial of diet in men with early stage prostate cancer: rationale and design of the Men's Eating and Living (MEAL) Study (CALGB 70807). Pending submission to *Contemporary Clinical Trials* (**Appendix 3**).

- Funding

- a. 2008: Hope for a Cure Foundation, \$10,000
- b. 2009: NCI R01 CA132951-01A1, \$2.5 million
- c. 2010: Prostate Cancer Foundation (PCF), \$300,000

- Employment and Research Opportunities Resulting Directly from this Award

- a. I was asked to write and chair a national study protocol for a major NCI-sponsored clinical research group, CALGB (**Appendix 1**).
- b. I was appointed to the national leadership team of the GU Committee of the Alliance for Clinical Trials for Oncology, formerly known as CALGB. My formal title is Cadre Leader for early prostate cancer. In this capacity, I oversee the development and execution of approximately 10 national clinical research studies for prostate cancer.
- c. I was appointed Chair of the GU Surgery Committee for the Alliance for Clinical Trials for Oncology, formerly known as CALGB. In this capacity, I help oversee the development and execution of approximately 15 national clinical research studies for prostate, kidney, and bladder cancer.
- d. As a direct result of the successful implementation of my diet and prostate cancer RCT, I was able to obtain NCI funding for a diet and bladder cancer RCT (U10 CA037447-25), the successful completion of which resulted in a peer-reviewed publication (**Appendix 4**).³

V. Conclusion

In summary, during the award period, I successfully expanded the research study described in the original SOW from a RCT involving 2 study sites and 200 patients to a RCT involving at least 45 study sites and 464 patients. As of September 24, 2013, the study had achieved almost 60% of its targeted accrual and was enrolling an average of 10 patients per month.

The expansion of the RCT required the drafting of a new study protocol and the obtainment of additional extramural funding. With the mentorship and collaboration of my colleagues at UCSD, Roswell Park Cancer Institute, and the Alliance for Clinical Trials in Oncology (formerly known as CALGB), I completed both of these tasks during the first two years of the award period. I helped secure almost \$3 million in additional funding. In addition, I presented an abstract based on the study at a national meeting.

During the last three years of the award period, I achieved substantial success in initiating, promoting, and running the trial. I oversaw the accrual of 269 patients nationally, 30 patients at the Moores UC San Diego Comprehensive Cancer Center, and 12 patients at the San Diego VA Hospital; regularly responded to regulatory review at the Moores UC San Diego Comprehensive Cancer Center and the San Diego VA Hospital; oversaw the completion of the first planned interim analysis of baseline prostate biopsy data, the results of which exceeded expectations; completed a manuscript for submission to a peer-reviewed journal; continued my regular participation in the Alliance for Clinical Trials in Oncology (formerly known as CALGB); continued to lead the national study protocol by coordinating regular contact with Alliance personnel, collaborators at participating sites, and revisions to the study protocol; and regularly updated Alliance members and leadership regarding the status of the trial at Alliance meetings in Chicago.

This award has greatly increased my national exposure among prostate cancer researchers, led directly to leadership positions in a NCI-sponsored clinical research network, and honed my clinical research skills through invaluable practical experience.

This study uniquely and simultaneously addresses two understudied yet highly topical themes in the treatment of prostate cancer: active surveillance and dietary intervention. The synthesis of these two aims—optimizing management of active surveillance patients through a diet-based intervention—represents a novel approach with a high potential for providing near-term patient benefits that would serve both the prostate cancer population and the broader public health.

The expanded RCT, moreover, is measuring several relevant outcomes not included in the original SOW, including genetic polymorphisms and six additional quality of life measures. In addition, we are collecting and storing extra blood samples on each study participant to promote biomarker discovery in this completely unique patient population (**Appendix 1**). The larger sample size, expanded number of secondary

outcomes, and additional blood samples increase the probability that this study will yield clinically meaningful results.

Finally, this study is the first national, Phase III trial designed to test a diet-based intervention for prostate cancer and the first non-industry sponsored trial designed to test an intervention of any kind in prostate cancer patients on active surveillance. As such, it holds the potential to substantially inform treatment paradigms for prostate cancer, particularly in patients with early stage, less aggressive forms of this disease.

VI. References

1. Parsons JK, Newman V, Mohler JL, Pierce JP, Flatt S, and Marshall J. Dietary modification in prostate cancer patients on active surveillance: a randomized, multi-center feasibility study. *BJU Int*, 101: 1227-1231, 2008. doi: 10.1111/j.1464-410X.2007.07365.x. Epub 2008 Jan 24
2. Parsons JK, Newman V, Mohler J, Pierce JP, Paskett E, and Marshall J. The Men's Eating and Living (MEAL) Study: A Cancer and Leukemia Group B pilot trial of dietary intervention for the treatment of prostate cancer. *Urology*, 72: 633-7, 2008. doi: 10.1016/j.urology.2007.11.050. Epub 2008 Feb 15
3. Parsons JK, Pierce JP, Natarajan L, Newman VA, Barbier L, Mohler J, Rock CL, Heath DD, Guru K, Jameson MB, Hongying L, Mirheydar HS, and Marshall J. A randomized pilot trial of dietary modification for the chemoprevention of non-invasive bladder cancer: The Dietary Intervention in Bladder Cancer Study (DIBS). *Cancer Prev Res*, 2013 Sep;6(9):971-8. doi: 10.1158/1940-6207.CAPR-13-0050. Epub 2013 Jul 18

VII. Appendices

- Appendix 1: National study protocol
- Appendix 2: Abstract
- Appendix 3: Manuscript pending submission to *Contemporary Clinical Trials*
- Appendix 4: Published manuscript of related trial

Appendix 1

Activation Date: 12/01/10
Includes Update #01

CANCER AND LEUKEMIA GROUP B

CALGB 70807

The Men's Eating and Living (MEAL) Study: A Randomized Trial of Diet to Alter Disease Progression in Prostate Cancer Patients on Active Surveillance

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with CALGB will participate through the CTSU mechanism as outlined below and detailed in the CTSU Logistical Appendix I.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Members' side of the website located at <https://www.ctsuo.org>. Enter CTEP-IAM user id and password where indicated.
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the CALGB. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to CALGB unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by CALGB. (generally via email but may be sent via fax or postal mail). Please send query responses and delinquent data to CALGB and do not copy the CTSU Data Operations. Query responses should be sent to CALGB via postal mail (no transmittal form needs to accompany response). Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

The Men's Eating and Living (MEAL) Study: A Randomized Trial of Diet to Alter Disease Progression in Prostate Cancer Patients on Active Surveillance

Eligibility Criteria**Preregistration:**

Biopsy-proven adenocarcinoma of the prostate, clinical stage \leq T2a diagnosed within 24 months.
 $< 25\%$ of biopsy tissue cores positive for cancer.

$\leq 50\%$ of any one biopsy tissue core positive for cancer.

Patients who have prostate cancer with distant metastases are not eligible.

Patients who have had prior treatment for prostate cancer by surgery, irradiation, local ablative or androgen deprivation therapy are not eligible.

Patients with a history of non-cutaneous malignancy in the previous 5 years are not eligible.

Patients must be able to read and comprehend English language text and be able to understand spoken English over the phone.

Life expectancy of at least 3 years.

Patients who are currently taking vitamin supplements including lycopene and beta-carotene are eligible.

Patients who are currently taking coumadin are not eligible.

Participants will be men aged 50 to 80 years.

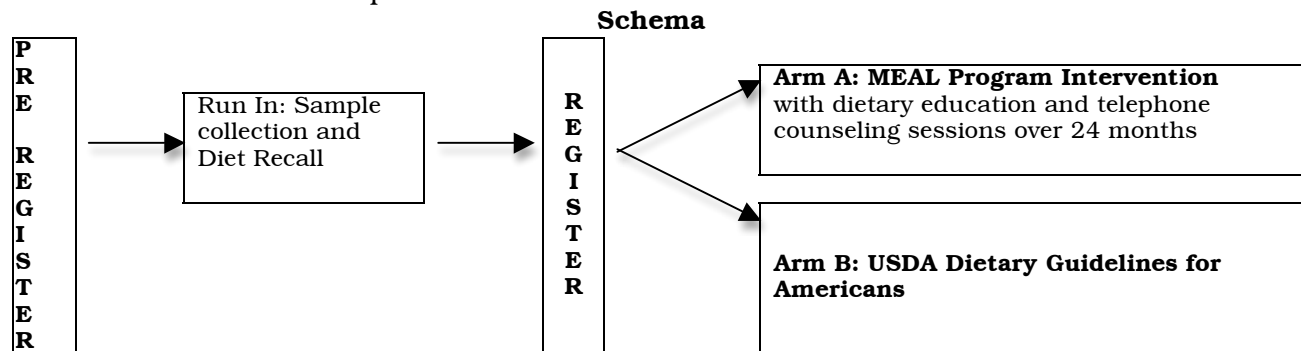
For men ≤ 70 years, biopsy Gleason score must be ≤ 6 ; for men > 70 years, biopsy Gleason score must be $\leq (3 + 4) = 7$.

Registration/Randomization:

Successful completion of three 24-hour dietary recalls during the run in period

Patients consuming ≥ 6 servings per day of fruits and vegetables (not including juices) are not eligible.

Submission of a blood sample.

**Stratification:**

- Age: Men ≤ 70 years; Men > 70 years
- Race: African American vs. Other
- Baseline Prostate Biopsy: 0-12 months prior to registration vs. >12 -24 months prior to registration

MEAL Program Intervention: The counseling protocol will be divided into four phases, with the first three phases completed in 7 months. The fourth phase will continue for 17 months.

The **first phase**, comprised of six counseling calls, will focus on education and the rapid development of self-efficacy.

The **second phase**, comprised of four calls over a 2-month period, will focus on practical and consistent implementation of the dietary pattern.

The **third phase**, comprised of four calls over a 4-month period, will help participants habituate to the dietary pattern by providing regular performance reviews.

The **fourth phase**, comprised of 8 calls over a 17-month period, will be a maintenance phase.

Quality of Life Measures: Seven quality of life measures will be used: Personal Habits Questionnaire, Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P); Memorial Anxiety Scale for Prostate Cancer (Max-PC); International Prostate Symptom Score (IPSS); Expanded Prostate Cancer Index Composite 26 (EPIC-26); Nutrition Self-Efficacy and Satisfaction with the MEAL Program.

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1.0 INTRODUCTION

1.1 Prostate Cancer: The Concept of Overtreatment

Prostate cancer is the most commonly diagnosed non-cutaneous cancer among US men. Approximately 192,000 new cases were identified in 2009 (1). Although prostate cancer is the second leading cause of cancer death among US men, the probability of dying from prostate cancer is relatively low. The lifetime risk of prostate cancer diagnosis is 16%, but the lifetime risk of death from prostate cancer is only 3% (1). This discrepancy between prostate cancer incidence and mortality, due in large part to detection of pre-symptomatic tumors by the prostate-specific antigen (PSA) assay, is distinct among cancers. As a result of widespread PSA testing, 50% of newly diagnosed prostate cancer patients now present with localized, lower-risk disease (2).

Most patients with lower-risk prostate cancer are treated with surgery or radiation (3). Although the probability of cure with these modalities is high, both are associated with urinary, bowel, and sexual morbidities that significantly diminish quality of life (4, 5). Moreover, despite the high probability that these men will remain disease-free, whether the treatments actually reduce prostate cancer-specific or overall mortality in lower-risk patients is not known. Many men with localized, higher-risk prostate cancer have aggressive disease that warrants aggressive intervention (6); many others, with lower-risk, generally indolent prostate cancer, even younger men likely to live 15 years or more from diagnosis, derive few, if any, survival benefits from treatment (7-10).

Population studies suggest that a substantial proportion of men diagnosed with lower-risk prostate cancer in the US are over-treated (2-4). In a recent study of the US SEER registry, Miller and colleagues concluded that approximately 50% of men with lower-risk prostate cancer received unnecessarily aggressive treatment, surgery or radiation (4). The staggering scope of this public health problem that is, unnecessarily aggressive treatment of lower risk prostate cancer, treatment that diminishes quality of life for tens of thousands of US men each year, challenges us to develop innovative therapeutic and diagnostic models to refine treatment paradigms within this patient population.

1.2 Active Surveillance (AS) for Lower-Risk Prostate Cancer

The concept that substantial proportions of men diagnosed with lower-risk prostate cancer are over-treated has fostered growing interest in a management approach known as active surveillance (AS). AS entails vigilant monitoring of men with localized, lower-risk prostate cancer by serial PSA measurements, frequent digital rectal examinations, and intermittent prostate biopsies. Intervention with surgery, radiation, or other therapies is reserved until patients show evidence of disease progression (9,11-16).

Active surveillance protocols for identification of patients with lower-risk disease vary by institution, but are generally similar. Clinical criteria for enrollment in a surveillance program typically include total PSA < 10 ng/mL, tumor that is non-palpable, or palpable but small on digital rectal examination (clinical stage T1 or T2) and lower-risk tumor characteristics on prostate biopsy, namely, low-grade (Gleason sum \leq 6) and low-volume (tumor evident only in a small number and percentage of biopsy cores) disease (9,11-16). Similarly, while there remains no clinical consensus, disease progression while on surveillance is broadly defined as a rapidly increasing PSA (manifested as decreased PSA doubling time or increased PSA velocity) or worrisome pathology on repeat biopsy (Gleason score \geq 7 or increased tumor volume) (9,11-16).

In carefully selected men with lower-risk prostate cancer, AS is a viable and safe treatment option. Warlick and colleagues, confirming earlier results (9), observed that patients followed on AS for up to 6 years who then progressed by PSA or pathological criteria and underwent surgery were just as likely to be cured of their disease as men who underwent surgery immediately after diagnosis (14).

Approximately 30% of patients on AS will progress based on current PSA or pathological criteria and thus receive intervention with surgery or radiation, typically within 2 years of beginning surveillance (11). The Hopkins data indicate that 31% of patients progress within 26 months (13, 15). In the Toronto cohort, 34% progressed after 64 months; however, the definition of progression for most of the follow-up period was based on a PSA DT of 2 years or pathology progression to Gleason grade 8. Klotz estimated that 20 percent of patients would progress on the basis of a PSA DT of 3 years, while 5 to 10% would progress on the basis of tumor grade progression. Moreover, up to 12% of men who do not meet objective criteria for progression will opt for intervention (11). Thus, in total, over 40% of men on AS will progress or proceed to treatment. Reducing the proportion of men who progress or choose treatment while on AS for prostate cancer represents a novel opportunity to minimize treatment-associated morbidity, improve patient quality of life, and contain health care costs.

1.3 Diet and Prostate Cancer

The existence of a distinct, relatively indolent phenotype in prostate cancer presents an important opportunity. A potential means of decreasing the number of men on AS who proceed to treatment is dietary change. There is great interest in the role of diet in the etiology and natural history of prostate cancer (17, 18). Accumulating evidence suggests that diet may alter prostate cancer initiation and progression. Macronutrients and micronutrients associated with decreased prostate cancer risk include retinoids, carotenoids (particularly lycopene), cruciferous vegetables, dietary fat, soy products, folate, retinol, vitamin D, and omega fatty acids (17-23). A range of phytochemicals in fruits and vegetables could have effects on a metabolically active organ like the prostate, and a number of plausible mechanisms have been proposed (24-39).

Experimental studies based on cell line and animal models suggest that vegetable intake may lessen the risk or retard the progress of prostate cancer. Rats fed tomato powder have decreased prostate-cancer specific mortality compared to controls (24) and, in vitro, lycopene inhibits DNA synthesis in prostate epithelial cells (25). Cell line and animal data support the anti-carcinogenic properties of isothiocyanates, which are components of cruciferous vegetables such as broccoli and cabbage. Isothiocyanates induce expression of cytoprotective phase 2 enzymes in multiple prostate tumor cell lines (26, 31) promote apoptosis of prostate cancer PC-3 cells in vitro, and inhibit growth of PC-3 xenografts in nude mice (28). In a prostatectomy model, men fed a tomato intensive diet had distinct biological changes potentially associated with suppression of prostate tumors (30).

Indirect evidence from epidemiology, ecological, case-control and cohort studies in humans suggests that altering nutritional intake may provide beneficial effects against prostate cancer (18). This evidence suggests a diet that emphasizes vegetable intake and de-emphasizes meat and fat intake may decrease the risk of prostate cancer initiation and progression. The most direct evidence for this supposition has been provided by studies of whole foods rather than micronutrients. Red meat and fat intakes tend to be associated with increased risk (particularly of aggressive cancer); cruciferous vegetables and tomatoes and tomato products tend to be most closely associated with decreased risk (20-23, 33).

Recent observational data also indicate that weight loss may alter the natural history of prostate cancer: among men in the Cancer Prevention Study II Nutrition Cohort, weight loss >11 lbs over 10 years was associated with a 40% reduction for high-grade cancer risk (34). Follow up of the Prostate Cancer Prevention Trial cohort indicated that a BMI > 30 kg/m² was associated with an 18% decreased risk of low-grade prostate cancer and a 29% increased risk of high-grade prostate cancer (35). Low serum cholesterol was associated in this same study with decreased risk of high grade prostate cancer (36).

To date, human experimental evidence supporting epidemiologic and pre-clinical findings, though intriguing, is limited. Isothiocyanates derived from cruciferous

vegetables enter the human prostate following oral consumption and may be associated with anti-carcinogenic, phase 2 enzyme activity in prostate tissue (29, 31). In a small intervention study, patients with recurrent prostate cancer experienced decreased PSA doubling times six months after beginning treatment with diet modification and stress reduction (37). In another small clinical trial of active surveillance patients, randomization to a plant-based diet with micronutrient supplements and intensive lifestyle changes resulted in decreased serum PSA concentrations, inhibition of prostate cancer cell growth, and progression to active treatment; (38) another non-randomized pilot study utilizing a similar intervention (plant based whole foods coupled with exercise and stress management) resulted in significant changes in prostate gene expression (39).

These studies provide preliminary clinical evidence that diet change may slow prostate cancer progression. Still, they were small studies with only short-term (~ 1 year) follow-up. Moreover, as it is impossible to isolate the effects of diet from those of exercise, stress management, and group support, these changes in PSA and cancer cell growth cannot with certainty be attributed solely to dietary change. On the other hand, the most likely factor driving these changes is diet. In addition, whether intensive lifestyle modifications such as exercise, yoga, and stress management would be practicable, sustainable behaviors in large groups of patients remain to be seen. An adequately powered trial, focusing on diet as a primary form of intervention, is needed.

We previously designed and implemented a telephone-based dietary intervention for prostate cancer patients based on well-established principles of social cognitive theory. This relatively straightforward intervention, the first to use diet change as a primary treatment for low risk prostate cancer, produced robust, beneficial diet changes (i.e. significantly increased vegetable intakes) and led to increased plasma levels of potentially anti-carcinogenic carotenoids in prostate cancer patients (40-42). We believe that the next step is to determine, in a suitable study sample, whether these diet changes, marked by increased plasma carotenoid levels, will exert a clinically relevant and sustainable effect on prostate cancer progression.

1.4 Dietary Intervention in an Active Surveillance (AS) Population

Men on AS represent a compelling population for studying diet change and prostate cancer for at least 4 reasons. First, approximately 100,000 men are diagnosed with lower-risk prostate cancer every year in the US. Some 42% of men on AS progress to treatment (30% because of disease progression, 12% because of anxiety); reducing this proportion represents a realistic and valuable therapeutic and public health goal (8, 9, 11, 13). Second, clinically localized, lower-risk cancer may potentially be more affected by dietary change than more advanced, aggressive disease. If diet is related to the risk of prostate cancer, it may well exert an impact on the earliest phases of prostate cancer; its impact may best be tested in an AS population. Third, AS patients are not receiving active therapy (i.e. radiation, surgery, or androgen) that would otherwise obscure or modify any beneficial effects of dietary change. Finally, AS patients would likely be receptive to nutritional interventions with proven benefits for cardiovascular and overall health (8, 11, 43).

Indeed, because prostate cancer diagnosis is a source of considerable anxiety and diminished quality of life for many patients diagnosed with lower-risk disease (44-46), dietary change might not only exert therapeutic biological effects on the tumor, but might also encourage men with lower-risk prostate cancer and no signs of progression to remain within an AS program. As previously noted, up to 12% of patients with no objective PSA or pathologic indications of progression nonetheless opt for treatment that may not improve their prognosis (11). Treatment preferences in this situation are generally believed to arise, to a large extent, from patient anxiety and discomfort over not receiving curative therapy. This attitude is likely fostered by the action-oriented approach that characterizes our current health care system (8). However, prostate cancer-related anxiety and its effects on treatment choice have not as yet been prospectively studied in an AS population.

Diet change presents an ideal opportunity for AS patients to alter the perception of their disease by providing an intervention on which to focus. This approach may dissuade otherwise lower-risk men from pursuing unnecessarily aggressive, morbidity-generating treatments. Such an approach would promulgate a novel therapeutic paradigm for lower-risk prostate cancer: medical management, without radical intervention, in a chronic disease state.

1.5 Quality of Life Among Prostate Cancer Patients

Cancer patients often report significant anxiety about their disease. Several investigators have documented fear of recurrence to be highly prevalent in a number of different cancer patient populations (47-50). Cancer survivors may experience lingering psychological sequelae, including fear of diagnostic tests and fear of recurrence for long periods of time after diagnosis and treatment (53).

Prostate cancer patients are not immune to worry over their disease (5, 44-46, 52, 53). However, treatment may also diminish fear of recurrence. Among prostate cancer patients undergoing definitive treatment, fear of recurrence peaked prior to treatment, then decreased within 6 months after treatment (52). A possible explanation for this finding is that patients were reassured about their prognosis after having undergone treatment. Providing prostate cancer patients the opportunity to exert control over a change in their dietary intake, a diet-based intervention may perhaps help patients overcome fear of recurrence, particularly if the intervention stabilizes PSA.

Part of the impact of a diet change program may involve social cognitive theory, which governs most current attempts to change behavior. A key element of social cognitive theory is self-efficacy. According to social cognitive theory, the interaction of the individual with the environment is influenced by his or her cognitions and beliefs about ability, expectation of behavioral outcomes, and evaluation and modification of behavior toward specific goals (54). Components of social cognitive theory include self-efficacy (confidence in ability to perform a particular behavior to accomplish a specific goal), outcome expectancies (belief that a particular behavior will result in a particular consequence), and self-regulation (adopting personal standards for behavior, appraising behavior against such standards, and creating incentives that motivate and guide behavior). Participating in diet change, as in this study, may increase patient feelings of self-efficacy, defined as their “judgments of their capabilities to organize and execute courses of action required to attain designated types of performance (55-57).” According to Bandura (56), mastery experiences are the most reliable source of efficacy information. Applied to this study, feelings of greater self-efficacy will increase patients’ ability to control their diet and consequently their health. Identifying and reinforcing patients’ present success is a factor that Bandura (54, 56), and Strecher and colleagues (58) suggest clinicians use to improve self-efficacy. Building a sense of self-efficacy is part of the MEAL program. Self-efficacy has been incorporated into various interventions: self-management interventions and educational programs in patients with chronic disease (61) and prostate cancer (57). Breast and colon cancer patients randomized to either an educational or nutritional intervention arm had significantly fewer depressive symptoms and better physical functioning than patients in the control group, primarily accounted for by self-efficacy (60). Cancer patients with greater self-efficacy have been found to be better adjusted and have a better overall quality of life (55, 57-59).

We expect that participating in the MEAL intervention will improve the quality of life for low risk prostate cancer patients. The literature is largely supportive, indicating that this intervention’s focus on self-efficacy will add measurably to quality of life (56-63). One of the implicit messages that participants take from being in this study will be that low risk prostate cancer is a condition to monitor, but neither a death sentence nor a condition that requires radical, immediate, life-changing intervention. We will not be able to compare trial participants to non-participants. We will,

however, be able to compare those randomized to the diet change to those randomized to the comparison group.

Low risk prostate cancer is a substantial public health issue that affects tens of thousands of men each year in the US. Epidemiologic, pre-clinical, and preliminary clinical studies suggest that diet is related to prostate cancer risk, so that changing to a high-vegetable diet may decrease prostate cancer progression in lower risk patients. Clearly, mature clinical data on use of diet to treat prostate cancer are lacking. We have developed a novel, practical, telephone-based intervention that has been shown to increase vegetable intake and serum carotenoid levels in men with prostate cancer. We propose to document the impact of this dietary intervention in an extended clinical trial using prostate cancer patients under AS; for such patients, the likelihood of treatment efficacy, even after delay, is relatively high. Patient anxiety is a prominent yet understudied complaint among AS patients; diet change may decrease prostate-cancer related anxiety among these patients. Further study of diagnosis-related anxiety will yield potentially important information for improving the psychological care of prostate cancer patients.

1.6 Pilot Data Supporting Dietary Intervention: The Women's Healthy Eating and Living (WHEL) Study for Breast Cancer

A CALGB pilot study demonstrated the feasibility of implementing dietary changes among cancer patients in the Women's Healthy Eating and Living study (WHEL), a multi-center trial of diet change for breast cancer (40-42,64). Utilizing well-established behavior change techniques, this intervention achieved substantial changes in vegetable, fiber and fruit consumption, along with a substantial change in fat consumption (64).

The dietary intervention we developed employs telephone-based communication. The conceptual framework of the intervention is derived from Social Cognitive Theory (54), which emphasizes strengthening of individual self-regulatory skills, including goal-setting, self-monitoring and evaluative judgments. We utilize lay coaches to help participants frame options for decisions. The coaches focus on self-efficacy, or participant belief that they can actually succeed in behavior change (64, 65). The lay coaches also provide a supportive environment for regular discussion of triumphs and failures as participants seek to change. The lay coaches are well versed in basic nutrition, and they are supervised by experienced and knowledgeable dietitians; nonetheless, they function less as authority figures than as facilitators or guides, and as supporters, helping participants optimize their options as they proceed through change (66).

The intervention efforts are timed so that they provide the greatest support and guidance when the challenges of change, hence the threats of failure, are greatest: at the beginning (65). We have demonstrated that major changes can be implemented during the first month of the intervention (40-42, 65). The subsequent challenge is to integrate change into the participant lifestyle, then to reinforce and maintain the change. The counselors during this time watch for signs that participant self-efficacy is waning; declining self-efficacy may be an indicator that failure is increasingly likely (65). We have shown that this approach results in substantial dietary change that can be maintained for several years (67).

This telephone-based approach has been shown to result in change that can be seen in accepted biomarkers of nutritional practice (40-42). Carotenoids, which are fat-soluble pigments found almost exclusively in vegetables and fruits, accumulate in blood. The most common of these, alpha carotene, beta-carotene, lutein, lycopene and cryptoxanthin, reflecting the intake of a wide range of plants, were used as general biomarkers of plant intake (65). The WHEL study intervention, on which our pilot trial was based, caused the diets and blood carotenoids of 1500 experimental subjects and 1500 control subjects to diverge substantially within a year of beginning the intervention; after that, we observed, over a period of 3 to 4 years, a slight decline in the difference between the dietary practices of experimental and control subjects (66). Nonetheless, experimental subjects in the WHEL study spent the bulk of their

study participation time consuming a diet that was radically different than both their pre-enrollment diet and that of comparison subjects.

A nuance of diet change trials is that subjects are not blinded to their assignment; thus, there is always a possibility that subject behavior will be changed by subject knowledge of intervention. In particular, experimental subjects may be inclined to exaggerate their compliance with diet goals. Subjects cannot, however, readily exaggerate their blood carotenoid levels except by changing their diet. These are integrated over an extended period, and experimental subjects are unlikely to change these other than by changing their diet.

While it is certainly true that any methodology involving prospective dietary change poses challenges, the WHEL data, and the to-be discussed MEAL data, indicate that we can profoundly change diet. In addition, these data confirm that comparison subjects will not in large part change their diets.

Although the effect of these changes on breast cancer recurrence was null for the overall study, a sub-group analysis based on hot flash status demonstrated significantly decreased risk of additional breast cancer events among women without hot flashes who had higher vegetable, fruit and fiber and lower fat intakes (70). These data tentatively support the notion that diet change may alter the natural history of breast cancer in select groups of patients.

1.7 The Men's Eating and Living (MEAL) Pilot Study

Based on the WHEL experience, we designed and implemented a pilot study of diet change in men with prostate cancer based on similar principles of behavior change: the Men's Eating and Living (MEAL) Study (40-42). This randomized, controlled clinical pilot trial of 74 men, most with clinically localized prostate cancer, utilized the same diet-change intervention outlined in this application. To increase the number of change patients for evaluation, we randomized 2 patients to intervention for every one randomized to comparison. This trial was different from the WHEL study, in that we invited the spouse or significant other of the patient, and not just the patient, to participate in the diet counseling. The study demonstrated that diet change with telephone-based counseling results in increased vegetable intake and increased plasma carotenoid concentrations among men with prostate cancer.

Dietary changes: vegetables

Consistent with counseling targets, vegetable intakes in the intervention arm increased significantly at six months, while those in the control arm remained static (Table 1). Diet was measured by a series of three 24-hour recalls collected interactively via telephone interview. In the intervention arm, mean daily intakes of total vegetables, crucifers, tomato products and other vegetables increased by 76%, 143%, 292%, and 55%, respectively. The intervention emphasized vegetable, rather than fruit intake, and white potatoes and lettuce did not count. As a result, fruit, lettuce, and potato intake declined for experimental subjects (40-42). In the control arm, there were no significant changes in mean intakes of total vegetables, crucifers, tomato products, lettuce and potatoes, or other vegetables.

Table 1. Vegetable intake* at baseline and 6 months as assessed by 24 hour dietary recall in the Men's Eating and Living (MEAL) Study

	Intervention n=45			Control n=23		
	Baseline	6 Months	Change	Baseline	6 Months	Change
Total vegetables	4.1	7.2	76%†‡	3.7	4.2	12%
Cruciferous vegetables	0.7	1.7	143%†‡	0.4	0.6	44%
Tomatoes	0.6	2.3	292%†‡	0.7	0.8	5%
Lettuce and potatoes	1.0	0.4	-58%†‡	0.6	0.6	-3%
Other vegetables	1.8	2.8	55%†	1.9	2.2	12%

*All intakes measured in servings per day

†Significant difference ($p < 0.05$) between groups

‡Significant difference ($p < 0.05$) within groups

Dietary changes: non-vegetables

Intakes of whole grains and beans in the intervention group increased, while fat intake decreased; mean daily intakes of whole grains and beans increased by 28% and 95%, respectively, while fat intake decreased by 12% ($p < 0.05$). In the control arm, whole grain and fiber intakes decreased by 33% and 21%, respectively ($p < 0.05$), and there were no significant changes in fruit, beans, fiber, or fat intakes (data not shown) (40-42).

Plasma carotenoid concentrations

Consistent with increased vegetable consumption, carotenoid concentrations increased in the intervention but not in the control group (Table 2). At baseline, plasma total carotenoid concentrations of intervention and control participants were virtually the same. At six months, however, those of intervention and control participants, respectively, rose by 26% and 3% ($p = 0.02$). In the intervention group, α -carotene, β -carotene, lutein, and lycopene concentrations increased significantly, while those in the control group remained static ($p < 0.05$). Cryptoxanthin levels changed in neither group. That the changes observed were qualitatively larger than those observed in such prevention interventions as the Polyp Prevention Trial (69) suggests that this test of dietary intervention might be much more sensitive and powerful than either the Polyp Prevention Trial or the Women's Health Initiative (70).

Although the MEAL study was not strictly intended for AS patients, the patients on AS (53% of the study sample) experienced dietary change and plasma carotenoid results identical to those for the entire group (42). These data support the feasibility of implementing a larger clinical trial of a telephone-based diet intervention in men with prostate cancer treated with AS.

Our data, which include blood-based biomarkers, indicate that experimental subjects changed their diets, but that comparison subjects did not. Other data, including the Polyp Prevention Trial (71) and the Women's Healthy Eating and Living study (66), confirm that comparison subjects in diet intervention trials in general do not change their diets to nearly the extent that experimental subjects do.

Table 2. Plasma carotenoid concentrations at baseline and 6 months in the Men's Eating and Living (MEAL) Study

Carotenoid (mmol/L)	Intervention n=45			Control n=23		
	Baseline	6 Months	Change	Baseline	6 Months	Change
α-Carotene	0.17	0.23	33%†	0.16	0.17	5%
β-Carotene	0.61	0.83	36%††	0.63	0.66	5%
Lutein	0.44	0.53	19%††	0.43	0.43	0
Lycopene	0.79	1.03	30%††	0.86	0.87	2%
Cryptoxanthin	0.19	0.17	-11%	0.17	0.18	11%
Total Carotenoids	2.21	2.79	26%††	2.24	2.32	3%

†Significant difference (p<0.05) between groups

††Significant difference (p<0.05) within groups

MEAL: Program satisfaction

The response to the intervention was almost universally positive. In a very preliminary attempt to document the extent to which the participants experienced this program positively, we administered a limited questionnaire to 33 of the participants. We asked them to describe their satisfaction on a 5-point scale, with 1 indicating strong dissatisfaction and 5 strong satisfaction. The responses were extremely positive; 31 of 33 rated their counselor a 5 for being prompt and convenient with sessions; 30 of 33 rated the counselor a 5 for listening; 32 of 33 rated the counselor a 5 for being easy to talk to; 29 of 33 rated the counselor a 5 for knowledge; 26 of 33 gave the counselor a 5 for being helpful; 25 of 33 gave the counselor a 5 for motivating them; and 24 of 33 gave the counselor a 5 for helping them to overcome barriers.

1.8 Study Design

In summary, these promising pilot data support the feasibility of a larger clinical trial of a telephone-based dietary intervention in men with prostate cancer treated with AS. The synthesis of these two aims-optimizing management of active surveillance patients through diet-represents a novel approach to this topic with a high potential for providing near-term patient benefits that would serve both the prostate cancer population and the broader public health. An adequately powered trial, focusing on diet as a primary form of intervention is needed.

CALGB 70807 is a randomized, phase III clinical trial designed to test this practical, diet-based intervention for prostate cancer in a broader clinical setting. Patients on AS will be randomized either to an intervention of centralized, telephone-based dietary counseling and structured dietary education or to a comparison control condition in which they receive the USDA Dietary Guidelines for Americans. Study endpoints will include disease progression, incidence of treatment, and health-related quality of life.

1.9 Inclusion of Women and Minorities

Because prostate cancer occurs primarily in men above the age of 50, recruitment of participants for this study will focus upon men aged 50 years and older. Since women and children are not subject to prostate cancer, they will be excluded from this study. Efforts will be made to enroll individuals of all races and ethnic backgrounds, with the added goal of recruiting relatively high numbers of individuals of Hispanic origin and of African-American origin. The increased risk of prostate cancer and especially of lethal prostate cancer among African Americans makes it imperative that we secure adequate representation of African Americans in this study.

CALGB has a long history of effort to ensure adequate representation of minorities in all clinical trials, including prevention trials. The recent experience of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (80) is instructive: 29% of the CALGB participants were African Americans. In our MEAL pilot study, 12% of participants were non-white. Our goal with the full MEAL trial is for 29% of participants to be members of racial minorities, especially African Americans.

Accrual Targets					
Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	0	+	32	=	32
Not Hispanic or Latino	0	+	432	=	432
Ethnic Category: Total of all subjects	0 (A1)	+	464 (B1)	=	464 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	4	=	4
Asian	0	+	5	=	5
Black or African American	0	+	79	=	79
Native Hawaiian or other Pacific Islander	0	+	4	=	4
White	0	+	372	=	372
Racial Category: Total of all subjects	0 (A2)	+	464 (B2)	=	464 (C2)

(A1 = A2)

(B1 = B2)

(C1 = C2)

Accrual Rate: 15 pts/month

Total Expected Accrual: 464 Min 464 Max

2.0 OBJECTIVES

2.1 Primary Objective

To determine if a telephone-based dietary intervention compared to no intervention will decrease clinical progression in AS patients.

2.2 Secondary Objectives

2.2.1 To compare the incidence of active treatment (surgery, irradiation, local ablation, or androgen deprivation) in AS patients receiving dietary intervention compared to no intervention.

2.2.2 To compare prostate cancer-related anxiety in AS patients receiving dietary intervention compared to no intervention.

2.2.3 To compare health-related quality of life in AS patients receiving dietary intervention compared to no intervention.

3.0 ON STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following might increase the risk to the patient entering this protocol:

- Patients with medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient should not be enrolled. Such conditions may include uncontrolled chronic diseases (including uncontrolled diabetes mellitus, cardiac disease, ulcerative colitis, and Crohn's disease); or psychiatric illness/social situations that would limit compliance with study requirements and/or prevent the patient from giving informed consent.
- Intolerance of cruciferous vegetables.
- Unwillingness to adopt a vegetable-intensive diet.

4.0 ELIGIBILITY CRITERIA

4.1 Preregistration Eligibility

4.1.1 Histologic Documentation:

- Biopsy-proven (consisting of ≥ 10 tissue cores) adenocarcinoma of the prostate diagnosed within 24 months prior to presentation.
- $< 25\%$ of biopsy tissue cores positive for cancer.
- $\leq 50\%$ of any one biopsy tissue core positive for cancer.
- Clinical stage $\leq T2a$.
- Patients who have prostate cancer with distant metastases are not eligible.

4.1.2 Prior Treatment

- Patients who have had prior treatment for prostate cancer by surgery, irradiation, local ablative (i.e. cryosurgery or high-intensity focused ultrasound) or androgen deprivation therapy are not eligible.

4.1.3 Patients who have had a history of non-cutaneous malignancy (other than non-melanoma skin cancer) in the previous 5 years are not eligible.

4.1.4 Language

- Patients must be able to read and comprehend English language text and be able to understand spoken English over the phone.

4.1.5 Life expectancy of at least 3 years.

4.1.6 Patients who are currently taking vitamin supplements including lycopene and beta-carotene are eligible.

4.1.7 Patients who are currently taking coumadin are not eligible.

4.1.8 Participants will be men aged 50 to 80 years.

4.1.9 For men ≤ 70 years, biopsy Gleason score ≤ 6 ; for men > 70 years, biopsy Gleason score $\leq (3 + 4) = 7$.

4.1.10 Required Initial Laboratory Values:

- Serum PSA < 10 ng/ml

4.2 Registration Eligibility

4.2.1 Successful completion of three 24-hour dietary recalls during the run in period.

4.2.2 Patients consuming ≥ 6 servings per day of fruits and vegetables (not including juices), as measured by a food frequency questionnaire at initial enrollment, are not eligible.

4.2.3 Submission of blood sample

5.0 REGISTRATION

5.1 Preregistration

Informed Consent: The patient must be aware of the neoplastic nature of his disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the study, alternatives, potential benefits, side effects, risks and discomforts.

Protected Health Information: In order to contact patients by telephone and by mail, it will be necessary to collect those participants' names, addresses, and telephone numbers. This information will be sent to the University of California, San Diego Moores Cancer Center and will be destroyed upon completion of the study.

CALGB Preregistration Procedures

This study uses the CALGB Web-based Patient Registration system. Preregistration must occur prior to providing patients with access to the online patient data entry site, login information, or training.

Confirm eligibility criteria (Section 4.0). Complete the Preregistration Worksheet. Access the Web-based Patient Registration system via the patient registration tab at www.calgb.org. If the registering CRA requires assistance, he/she may consult the on-line help file located at the bottom of the screen or call the IS Help Desk at 1-888-44CALGB. If further assistance is required, the registering CRA may call the CALGB Registrar (919-668-9396, Monday-Friday, 9 am – 5 pm, Eastern Time; Registration fax 919-668-9397). Enter the following information:

Study

Name of group (CALGB)

Name of institution where patient is being treated

Name of treating physician

Physician's email address

Physician's telephone contact information

Name of treating research nurse

Research nurse's email address

Name of responsible CRA

Responsible CRA's email address

CALGB patient ID #

Patient's first name, middle initial, and last name

Patient's Social Security #, date of birth, and local hospital ID #

Patient's gender

Patient's age

Patient's race

CTC performance status

Disease, type and stage

CALGB treatment trial #

Clinical trial treatment start date

Date of signed consent

Eligibility criteria met (no, yes)

When the patient is preregistered, a patient identification number will be generated, which will be kept in the records.

The Main Member/At-Large Institution and registering institution will receive a Confirmation of Preregistration which will be checked for errors. Corrections will be submitted in writing to CALGB Statistical Center, Data Operations, Hock Plaza, 2424 Erwin Road, Suite 802, Durham, NC 27705.

Within 24 hours of preregistration, fax the MEAL Contact Information Form C-2010 to Vicky Newman at 858-822-6896, in addition, notify Vicky Newman via email at vinewman@ucsd.edu.

5.2 Run-In

Patients will complete the Personal Habits Questionnaire and provide baseline 6-hour fasting blood samples.

Within one week of receiving the contact sheet from sites, patients will be called by the nutrition unit at UCSD on randomly selected days to complete three 24-hour dietary recalls. The series of dietary recalls will be completed within 2-3 weeks. Participants will have two chances to successfully complete the run-in.

5.3 CALGB Registration/Randomization Requirements

Upon completion of the run-in, UCSD will notify the site and the statistical center about patient eligibility. Eligible patients who completed the run-in and submitted a blood sample, will then be registered and randomized by the site.

This study uses the CALGB Web-based Patient Registration system. Randomization will be accepted only through CALGB Main Member Institutions, at-large members, selected affiliate institutions and CCOPs using the Web-based Patient Registration system. Registration must occur prior to the initiation of therapy.

Confirm eligibility criteria (Section 4.0). Complete the Registration Worksheet. Access the Web-based Patient Registration system via the Patient Registration tab on the CALGB Member Website at www.calgb.org. If the study does not appear on the list of studies in the Patient Registration system, the registration must be performed by the CALGB Registrar via phone or fax. If the registering CRA requires assistance, he/she may consult the on-line help file at the bottom of the screen or call the IS Help Desk at 1-888-44CALGB. If further assistance is required, the registering CRA may call the CALGB Registrar (919)-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time. Enter the following information:

CALGB patient ID #, if applicable

Study

Name of group (CALGB)

Name of institution where patient is being treated

Name of treating physician

Name of person in contact with the patient record (responsible contact)

Protocol IRB approval date

Date of signed consent

Treatment Start Date (if applicable)

Date [of] HIPAA authorization signed by the patient

Patient's initials (last initial, first initial, middle initial)

Patient's Social Security #, date of birth, hospital ID #, and survival status

Patient's gender

Patient's race

Patient's ethnicity

ECOG performance status

Patient's height (cm) and weight (kg) (if applicable)

Type of insurance (Method of Payment)

Patient's postal code

Disease, type and stage, if applicable

Eligibility criteria met (no, yes)

When the patient is registered, a CALGB patient identification number will be generated. Please write the number in your records. Registration to treatment studies will not be completed if eligibility requirements are not met for all selected trials.

After registration is complete, the patient may be randomized. The patient is randomized according to the stratification factors, which must be entered to obtain a treatment assignment. Once the randomization is complete, note the patient's treatment assignment in your records. Please fax registration/randomization information to Vicky Newman at 858-822-6896 with notice also by email to vinewman@ucsd.edu. Upon receipt of this information, patients will be contacted by UCSD staff for their initial orientation telephone call. Patients will also receive an enrollment packet, provided by UCSD, which will contain either information about the intervention or a packet of NCI-endorsed nutritional intervention materials (see Section 8.3).

The Main Member Institution and registering institution will receive a Confirmation of Registration and a Confirmation of Randomization. Please check both confirmations for errors. Submit corrections in writing to the data coordinator at the CALGB Statistical Center, Data Operations, 2424 Erwin Rd, Ste 802 Hock Plaza, Durham, NC 27705, or fax to 919-668-9397.

5.4 Stratification Factors

1. Age
 - a) Men \leq 70 years b) Men > 70 years
2. Race
 - a) African American b) Other
3. Baseline Prostate Biopsy
 - a) 0-12 months prior to registration b) >12-24 months prior to registration

6.0 DATA SUBMISSION AND SAMPLE SUBMISSION

6.1 Data Submission: Forms should be submitted to the CALGB Statistical Center, Data Operations, in compliance with the Data Submission schedule below. There are three options for submitting forms that use the Teleform barcode and cornerstones:

- The preferred method is to submit the forms electronically using the "Submit to CALGB" button located at the bottom of the last page of each form. Forms submitted electronically should not be submitted by fax or mail.
- The forms may be faxed to 919-416-4990. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- The forms may be mailed to the CALGB Statistical Center, Data Operations, Hock Plaza, 2424 Erwin Road, Suite 802, Durham, NC 27705. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

Data Submission: Submit forms to the CALGB Statistical Center, Data Operations at the following intervals:

Forms		Submission Schedule
Pre-Registration		
	Pre-Registration Worksheet	Submit at pre-registration
C-2010	MEAL Contact Information	Submit MEAL contact information to the UCSD staff (See Section 5.1)
Run In		
C-2002	Personal Habits Questionnaire	Submit within 2 weeks of registration
Registration		
	Registration Worksheet	Submit within 2 weeks of registration
C-2012	CALGB 70807 On Study Form	
Quality of Life		
C-2003	CALGB 70807 MAX-PC Form	Submit within 2 weeks of registration
C-2004	CALGB 70807 Nutritional Self Efficacy Form	
C-2005	CALGB 70807 IPSS Form	
C-2023	CALGB 70807 EPIC-26 Form	
C-2007	CALGB 70807 FACT-P Form	
During Intervention		
C-2003	CALGB 70807 MAX-PC Form	Submit at 6, 12, 18 and 24 months
C-2004	CALGB 70807 Nutritional Self Efficacy Form	
C-2005	CALGB 70807 IPSS Form	
C-2023	CALGB 70807 EPIC-26 Form	
C-2007	CALGB 70807 FACT-P Form	
C-2008	CALGB 70807 MEAL Evaluation	Arm A patients only: Submit at 24 months
C-2013	CALGB 70807 Follow Up Form	Submit at 3, 6, 9, 12, 15, 18, 21, 24 months
Post Intervention Follow-Up		
C-2013	CALGB 70807 Follow Up Form	Submit every 3 months until 2 years from date of registration (see Section 8.7)
Other		
C-260	CALGB Remarks Addenda	Submit as needed

6.2 Sample Collection and Submission

All participating institutions must collect samples for patients enrolled on CALGB 70807. Biomarker and pharmacogenomic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 10.0. Tissue and blood will be collected at the following time points for these studies:

	Preregistration*	12 Mos	24 Mos	Submit To:
H&E slides	X	X	X	PCO
Plasma (10 ml Green top tube)	X	X	X	PCO
Serum (10 ml Red top tube)	X	X	X	PCO
Whole Blood (10 ml Lavender top tube)	X			PCO

* To be completed during the run-in period.

All submitted specimens must be labeled with the protocol number (70807), CALGB patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

Specimens for patients registered on this study must be logged and shipped using the online CALGB Specimen Tracking system. All institutions may access this system via the CALGB Web site, <http://www.calgb.org>.

A copy of the Shipment Packing Slip produced by the CALGB Specimen Tracking System must be printed and placed in the shipment with the specimens.

USE OF THE SPECIMEN TRACKING SYSTEM IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

For procedural help in logging and shipping specimens, please refer to the Specimen Tracking System User Guide, which can be accessed via the Help link within the Specimen Tracking System.

To report technical problems with the CALGB Specimen Tracking System, such as login issues or application errors, and/or for further assistance using the application, please contact the CALGB Help Desk at 877-44CALGB or calgb-support@calgb.duhs.duke.edu.

Instructions for the collection and shipping of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Samples should be shipped Monday-Friday by overnight service to assure their receipt. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday Delivery." Do not ship specimens on Saturday.

All specimens should be sent to the following address:

CALGB Pathology Coordinating Office
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073
Fax: 614-293-7967

6.2.1 Serum/Plasma/Whole Blood Preparation

First prepare the vacutainer tubes for protection from light by wrapping aluminum foil around the tube prior to filling it or putting it in a red or amber colored specimen bag. After drawing the tube, gently invert it once or twice to mix the additive with the blood. Immediately replace the sample into the previously prepared aluminum foil slip or place it into the red or amber colored specimen bag.

Throughout all stages of blood processing, shipping, and handling, it is very important to prevent prolonged exposure of blood samples and separated blood components to light. Work quickly and efficiently. When samples and sample components must be set aside, cover them or put them away from light.

6.2.2 Whole blood processing

Draw 10 mL of whole blood in a lavender top (EDTA coagulant) tube and keep refrigerated until shipped overnight to the CALGB PCO. Label the tube with the patient's initials, CALGB/CTSU patient ID number, study number (CALGB 70807), and date of collection. The sample should be shipped the same day on a cold pack by overnight mail to:

CALGB Pathology Coordinating Office
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Phone: 614-293-7073 FAX: 614-293-7967

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

6.2.3 Plasma processing

Draw 10 mL of whole blood in a green top (heparin coagulant) tube. As described above, throughout all stages of blood processing, shipping, and handling, it is very important to prevent exposure of the blood to light. Bring the vacutainer tubes to the processing room inside the foil wrap, the red bag, or the amber bag. Try to start the process within 30 minutes of collection. If this is not possible, the tube(s) should be refrigerated until centrifugation.

Before you start the centrifugation, make sure the brake is off, the speed is set between 2,400 - 2,800 rpm, the temperature is 4-degrees C to 8-degrees C and the centrifugation time is set at 10 minutes.

After centrifuging for 10 minutes, allow the centrifuge to come to a complete stop before opening the cover. Do not use the brake as it may cause the red blood cells to become re-suspended in the plasma. Any tube containing red blood cells in the plasma should be re-centrifuged. Immediately return the tubes to the light protection device (aluminum foil pouch or red or amber bag).

The plasma should be aliquotted into cryovials* within 15 minutes after centrifuging. All plasma samples will be pipetted as 0.8 ml amounts into the cryogenic storage vials* Place the samples in the -70-degrees C freezer as soon as possible after aliquotting. Samples must be frozen at least 2 hours before packing them for shipment. If a -70-degree C freezer is unavailable, the cryovials can be placed in a -20-degree C freezer immediately after aliquotting, and then transferred to a -70-degree C freezer as soon as possible, but no longer than 2 days (over the weekend). Placing the samples on wet ice or dry ice does not sufficiently preserve the sample; at least a -20-degree C freezer is required. Samples may NOT be thawed after freezing.

* Cryovial Choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

6.2.4 Serum processing

Draw 10 mL of whole blood in a red top tube. As described above, throughout all stages of blood processing, shipping, and handling, it is very important to prevent exposure of the blood to light. Gently invert 5 times to mix clot activator with blood. Let blood clot for 30 minutes. Observe a dense clot.

Bring the vacutainer tubes to the processing room inside the foil wrap, the red bag, or the amber bag. Try to start the process soon after 30 minutes of collection. If this is not possible, the tube(s) should be refrigerated until centrifugation.

Before you start the centrifugation, make sure the brake is off, the speed is set between 2,800 - 3,000 rpm, the temperature is 4-degrees C to 8-degrees C and the centrifugation time is set at 10 minutes.

After centrifuging for 10 minutes, allow the centrifuge to come to a complete stop before opening the cover. Do not use the brake as it may cause the red blood cells to become re-suspended in the serum. Any tube containing red blood cells in the serum should be re-centrifuged. Immediately return the tubes to the light protection device (aluminum foil pouch or red or amber bag).

The serum should be aliquotted into cryovials* within 15 minutes after centrifuging. All serum samples will be pipetted as 0.8 ml amounts into the cryogenic storage vials* Place the samples in the -70-degrees C freezer as soon as possible after aliquotting. Samples must be frozen at least 2 hours before packing them for shipment. If a -70-degree C freezer is unavailable, the cryovials can be placed in a -20-degree C freezer immediately after aliquotting, and then transferred to a -70-degree C freezer as soon as possible, but no longer than 2 days (over the weekend). Placing the samples on wet ice or dry ice does not sufficiently preserve the sample; at least a -20-degree C freezer is required. Samples may NOT be thawed after freezing.

* Cryovial Choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

When you are ready to ship the plasma and serum specimens to the Pathology Coordinating Office, see Section 6.2.5 for packing instruction:

6.2.5 Packing and Shipping Instructions

- (1) Place dry ice nuggets on the bottom of the insulated shipping container.
 - (2) Place each freezer box in a sealed plastic bag. Remove as much air as possible from the bag before sealing.
 - (3) Place the sealed bags in the insulated shipping container on top of the dry ice.
 - (4) Layer additional* dry ice on top of and around the plastic bags. Place any remaining freezer boxes in sealed plastic bags on top of the dry ice.
- * Overnight deliveries should contain about 10-12 lbs. of dry ice. This will allow the package to remain frozen for 48 hours in case the shipment is delayed.
- (5) Seal the shipping fiberboard box tightly and tape all seams with waterproof tape. To delay thawing, place the box in the -70-degree C freezer to await pickup. This step need not be done if the box is packed within 2-3 hours of pickup.

Ship specimens to:

CALGB Pathology Coordinating Office
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Phone: 614-293-7073 FAX: 614-293-7967

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

6.2.6 Submission of H&E Stained Prostate Biopsy Slides

Pathology specimens will be collected for confirmation of prostate pathology. Prostate biopsy slides will be submitted at baseline, 12 and 24 months with a minimum of 10 tissue cores obtained utilizing a standard, extended biopsy pattern. If, at the discretion of the treating physician, a patient undergoes additional prostate biopsies at a time other than 12 or 24 months, the prostate biopsy slides from these additional prostate biopsies should be submitted as well. **Representative stained hematoxylin and eosin (H&E) diagnostic slides from each biopsy site/container will need to be forwarded to the PCO for review.** Submission of paraffin embedded tissue blocks is not required. Submission of the local pathology report is required. The local pathology report should contain the number of cores obtained for each biopsy to allow central verification that ≥ 10 cores were obtained for each biopsy.

Biopsy slides will be reviewed by Dr. Peter Humphrey at Washington University. The PCO will scan the slides and upload the images to a website and Dr. Humphrey will review the scanned images. He will forward his evaluation to the Statistical Center.

7.0 REQUIRED DATA**Guidelines for Pre-Study Testing**

To be completed within 3 months before preregistration

- Baseline PSA

To be completed within 24 months before preregistration

- Prostate Biopsy Tissue

	Preregis- tration	Run- in	Regis- tration	Month							
				3	6	9	12	15	18	21	24
Test and Observations											
History and Physical	X			X	X	X	X	X	X	X	X
Height†	X										
Weight†	X			X	X	X	X	X	X	X	X
DRE	X						PRN				PRN
Diet Recall		A					A				A
Labs and Staging											
PSA	X			X	X	X	X	X	X	X	X
QOL Instruments											
Personal Habits Questionnaire		X									
MAX-PC			X		X		X		X		X
Nutrition Self- Efficacy*			X		X		X		X		X
IPSS			X		X		X		X		X
EPIC-26			X		X		X		X		X
FACT-P			X		X		X		X		X
MEAL Program Satisfaction*											X
Sample Submission											
Blood: Carotenoid Analysis		X					X				X
Prostate biopsy tissue	X						X				X

A To be conducted by UCSD staff.

* Only to be administered to patients randomized to Arm A.

† Refer to Section 8.1 for height and weight measurement instructions.

8.0 INTERVENTION

The principal strategy to promote dietary change in the intervention arm will be a telephone counseling protocol with individualized, one-on-one assistance tailored to each participant. The intervention will last 24 months. Intervention participants will engage in a series of telephone-based diet counseling sessions throughout the study. The first phase of sessions will guide initial diet-change attempts, the second will help participants complete their diet changes, and the third and fourth phases will enable participants to maintain and monitor their diet changes. This highly structured, computer-assisted telephone counseling protocol will facilitate standardization of the intervention.

8.1 Preregistration

At preregistration participants will complete a contact sheet that will be faxed to UCSD within 24 hours of preregistration.

Urologic Assessment

At initial assessment, participants will be evaluated in a urology clinic by a urologist in clinic as per typical AS protocols and current standard of care (2-4, 11, 13). Urological evaluations will be conducted by the GU Investigator or appropriate designee at each site. The baseline visit will include a DRE to confirm clinical stage. DRE will entail palpation of the posterior and posterolateral aspects of the entire prostate in the standard fashion.

Height and weight must be obtained during preregistration. Below are recommended guidelines to obtain these measurements in an accurate manner.

Weight: Weigh each participant on a medical balance or electronic scale in light clothing without shoes. Each participant should be weighed on the same scale throughout the study. Place the scale on a level uncarpeted floor surface. Before each weighing, check the scale to confirm that it reads zero in the absence of a load, and if necessary adjust it to read zero. If the participant's feet are bare, one may place a disposable paper towel on the scale platform. Ask the participant to stand still on the scale platform, arms down at their sides, and feet centered on the platform with weight evenly distributed. Record weight to the nearest pound.

Height: Measure the participant's height without shoes, using a stadiometer. Ask participant to stand up with heels together and weight equally distributed. Ideally, participants heels, buttocks, shoulders, and head should all touch the vertical board; however, in some cases this may not be possible. In this event, take the measurement with buttocks and heels touching the vertical board, or with head and buttocks touching the vertical board. Ask the participant to breath in deeply at which juncture the movable headboard should be placed on the head with only enough pressure to slightly compress the hair. Record height to the nearest 0.25 inch, rounding down.

8.2 Run-In

Patients will then complete the Personal Habits Questionnaire from the Women's Health Initiative (66) and provide 6-hour fasting blood samples. Eligible patients will be contacted by staff of the Moores Cancer center within a week to schedule a series of three 24-hour dietary recalls which will be completed within 3 weeks.

8.3 Registration/Randomization

Upon completion of the run-in, UCSD will notify the site and the statistical center about patient eligibility. Eligible patients who successfully completed the run-in, consumed fewer than 6 servings of fruits and vegetables (not including juices) per day and submitted a blood sample, will then be randomized.

After randomization, all patients will participate in a 5-10 minute telephone orientation conducted by staff from the Moores UCSD Cancer Center. The orientation call for intervention participants randomized to Arm A will explain the counseling program, the dietary targets, and the scientific rationale supporting these targets. During this call, participants will be introduced to the "Participant Notebook" which provides written material describing the counseling program. The notebook outlines the dietary targets, offers supporting information on strategies to achieve these targets, supplies reference tools to help participants accurately estimate servings of target foods, and offers recipes and articles about diet and prostate cancer. Patients randomized to Arm B will be sent the USDA Dietary Guidelines for Americans.

All counseling will be performed by telephone from the Moores UCSD Cancer Center using a counseling program and infrastructure of personnel developed during the WHEL (68) and MEAL (40, 42) studies. The protocol will follow a step-wise, phased approach employing strategies adopted from social cognitive theory. Motivational interviewing techniques will be utilized to help patients maintain responsibility for their own behavior change.

Each participant in Arm A will be assigned to a personal counselor/coach; if the participant has a spouse or significant other, the counselor/coach will also seek to enlist his or her cooperation and support. Counselors will work morning, afternoon, or evening shifts, and every effort will be made to assign participants to a counselor working when they prefer to receive calls. Call length will range from 20-40 minutes. Calls will be more frequent and of longer duration during the early phases of counseling.

Educational materials will be sent to patients on a schedule that supports the behavioral intervention goals. The participant notebook that patients enrolled on Arm A receive will include background material on dietary targets, as well as monitoring forms that patients can use to monitor their dietary change.

In order to maintain participant morale, UCSD staff will provide 8 regularly scheduled newsletters to participants on both arms of the study over the course of 24 months. Each newsletter will be two pages and will contain information about diet and healthy lifestyle. Patients enrolled on the experimental arm, will receive newsletters that will focus on study goals and progress and will provide tips on achieving and maintaining diet change. The newsletters will also include information on diet and cancer, the challenges of diet change and the advances in prostate cancer control. New recipes will also be included in these newsletters. Patients enrolled to the comparison arm will receive newsletters that provide general information about diet. The content of both intervention and control newsletters will vary depending on how long the patient has been on study and new information that becomes available.

8.4 Clinic Visits

History & Physical (Every 3 Months)

Participants will be evaluated in a urology clinic at initial assessment and every 3 months thereafter by a urologist in clinic as per typical AS protocols and current standard of care (2-4, 11, 13). Patients must be weighed and their height measured according to the instructions in Section 8.1. Urological evaluations will be conducted by the GU Investigator or appropriate designee at each site. The baseline visit will include a DRE to confirm clinical stage. Since PSA and biopsy changes are much more sensitive for detecting clinical progression than changes in prostate examination among patients on AS (11), subsequent DRE will be performed at the discretion of the individual urologist. These results will not be used to define progression.

PSA Measures (Every 3 Months)

Serum PSA levels will be measured at baseline and at every 3 months thereafter. PSADT will be calculated as \log_2 divided by the slope (the least squares estimator) of \log (PSA) observations over time using the last three PSA measurements (44, 83, 100). An example of a PSADT calculator can be found at www.ASURE.ca.

Prostate Biopsy (12, 24 Months)

Prostate biopsy will be performed by the treating urologist at 12 and 24 months with a minimum of 12 tissue cores obtained utilizing a standard, extended biopsy pattern. This practice is consistent with current standard of care in the urological community. The urologist or the participant will have the right to secure a biopsy earlier than 24 months. Although DRE is commonly used in oncologic practice, it is not highly quantifiable for men with the very small, often non-palpable tumors of our study participants.

Blood Sample Submission (12, 24 Months)

Blood samples will be collected at baseline, 12 and 24 months and will be submitted to the CALGB PCO (see Section 6.2.1) and analyzed for carotenoid concentrations.

Quality of Life Instruments (Every 6 Months)

Seven quality of life measures will be used: Personal Habits Questionnaire will be completed at run-in only, the Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P); Memorial Anxiety Scale for Prostate Cancer (Max-PC); International Prostate Symptom Score (IPSS); Expanded Prostate Cancer Index Composite 26 (EPIC-26); and the Nutrition Self-Efficacy will be completed at baseline and every 6 months. Finally, the Satisfaction with the MEAL Program form will be completed at 24 months (see Section 9.0).

8.5 Dietary Recall

Diets will be evaluated at baseline and at 12 and 24 months by a series of three separate 24-hour dietary recalls collected interactively via telephone interview conducted by the Moores Cancer staff. These telephone interviews will last approximately 20 minutes. Patient recalls will be performed on three randomly selected days over a three-week period and include two weekdays (Monday through Thursday) and one weekend (Friday through Sunday). Data will be catalogued and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition Coordinating Center, University of Minnesota).

8.6 Telephone Counseling Intervention (Arm A Only)

The counseling intervention will be divided into four phases, with the first three phases completed in 7 months. The fourth phase will continue for 17 months. Each counseling call will take an average of 30 minutes.

Phase 1: The first phase, composed of six counseling calls, will focus on education and the rapid development of self-efficacy skills. During this phase, frequent counseling sessions (every 3-4 days) will focus on short-term goals, emphasizing to participants and partners that the study dietary pattern can be compatible with their lifestyle. The counselor will monitor self-reported dietary intake interactively using dietary analysis software (The Food Processor for Windows, Version 7.8, ESHA Research, Salem, OR) to help the participant evaluate his performance and encourage him to concentrate on the positive aspects of his achievements before setting new sub-goals. Throughout this phase (and all other phases), counselors will encourage participants to report any difficulties in adopting the dietary pattern, and dietary targets will be adjusted accordingly to maximize chances of success.

Phase 2: The second phase, composed of four calls over a 2-month period, will focus on practical and consistent implementation of the dietary pattern. Counselors will help participants make structural changes to their food environments, such as altering the type of food available in the house, modifying recipes and patterns of food preparation, and focusing on portion sizes. Participants will learn to monitor their performance regularly, as counselors encourage goal setting and review.

Phase 3: The third phase, composed of four calls over a 4-month period, will help participants habituate to the dietary pattern by providing regular performance reviews. Studies of behavior change demonstrate that a declining sense of self-efficacy is associated with vulnerability to relapse. During this phase, social guidance and assistance in evaluating performance will be used to maintain interest in behavior maintenance, even as the level of necessary social guidance declines.

Phase 4: The counselors will regularly check on progress (8 calls over a 17-month period), providing positive feedback on achievements in maintaining the study targets while monitoring for warning signs of declining interest or self-efficacy. Ensuring participants that they can maintain the change they have implemented will still be critical. Intervention contacts will take place once every other month by those in Arm A only.

Dietary Targets: Participants in the intervention arm will be encouraged to achieve a challenging but attainable dietary pattern: 7 servings per day of vegetables (2 cruciferous, 2 tomato products, 3 other vegetables), 2 servings per day of whole grains, 1 serving per day of beans or other legumes, and 2 servings per day of fruit. Vegetable juice will be promoted as a means of increasing vegetable nutrients without the potential gastrointestinal problems of very high fiber intake. As vegetable intake appears most strongly associated with protection, the intervention will emphasize vegetable intake.

To maximize intake of the most bioactive nutrients and phytochemicals, intervention participants will be instructed to omit fruit juice, iceberg lettuce, and white potatoes from their calculations of plant servings. Counselor/coaches will emphasize colorful vegetables along with strong-flavored produce (cruciferous vegetables, onions, garlic), since strong flavor is an indicator (albeit crude) of phytochemical concentration. Within the context of these overall dietary targets, participants will be guided to obtain an adequate intake of all essential nutrients.

8.6.1 Quality control

Quality control will be enhanced by providing the telephone counseling from a centralized location at the Moores UCSD Cancer Center, thus enabling weekly case management meetings and flexibility in scheduling. Dietary counselors will be hired based on their demonstrated communication skills, telephone manner, knowledge of food and nutrition, and their enthusiasm for achieving the study dietary targets. Counselors will complete an intensive 80-hour training program addressing the rationale for the study, protocols for conducting 24-hour dietary recalls, the principles and practice of motivational interviewing and review of a random selection of recorded calls.

All counselors will practice extensive role-playing before conducting their first coaching session. This training will be overseen by the UCSD behavior change study team; the team has been involved in a multitude of behavior change studies.

We have developed a detailed, relational database that provides counselors with a computer-assisted coaching protocol for their participant contacts. All contacts will be recorded in the database, and the database will generate the call schedule for each counselor each day. Calls will then follow a script that includes suggested question phrasing and responses to key questions inserted into the database in real time; these standardize intervention delivery. Automatic range checks will ensure quality in the dataset. At the completion of each call, the counselor will be prompted for detailed comments that can be used in the next contact. These comments will be reviewed by the supervisor as a component of performance review. Each counselor's performance will be compared to that of his or her peers, in terms of achieving dietary change toward study goals and in keeping the database complete.

The database will provide weekly management reports to focus on key aspects of study progress, including delinquent data collection. The database will help us monitor regularly scheduled study operations, to comply with aspects of the protocol. For example, study reports will be generated, as needed, to identify intervention participants who have not been contacted as scheduled in the protocol. The reports will be provided to the counselors to help keep them on schedule, and to ensure that participants with lagging performance or possibly lagging interest do not drop out of the study.

To maximize effectiveness of the intervention, we will seek participant permission, in advance, to monitor calls. We will then monitor 10% of calls. The calls will be audio-taped and reviewed by peers and by supervisors to ensure that the intervention is standardized across participants. Throughout the study period, weekly case-management sessions will be conducted; supervisors, study investigators and counselors will use these to resolve challenging issues that have emerged.

A registered dietitian will supervise the telephone counseling intervention team. Counselors will also attend monthly 2-hour meetings which will include updates on study progress and in-service training on nutrition and behavior change counseling. On a quarterly basis, counselors will be provided with an assessment of their caseload's adherence to the dietary targets as a means of maintaining or improving performance. Together, these procedures, have contributed to the success of the WHEL (68) and MEAL (40-42) interventions.

8.7 Completion of Intervention

All patients are expected to participate in the diet intervention for 24 months.

8.7.1 Off Treatment Criteria

Off-Treatment criteria will include the following: 1) physician determination that continuation of the diet is medically contraindicated, 2) participant decision to withdraw from the dietary intervention, or 3) participant death.

Participants who wish to continue on the intervention even after meeting the criteria for progression will be permitted to do so.

Follow-up evaluations will continue for the duration of the study for all living participants.

8.7.2 Clinical Criteria for Progression and Active Treatment

The primary outcome of interest in this prevention trial is disease progression defined by (a) PSA doubling time (PSADT) less than 3 years, (b) PSA above 10 at any time, or (c) Gleason score on repeat biopsy ≥ 7 for men younger than 70 years and $\geq 4+3 = 7$ for men 70 years or older. These criteria are drawn from one of the largest active surveillance studies to date, the Toronto cohort (12).

Participants who do not meet PSA or biopsy criteria for progression are strongly encouraged to remain on AS while in the study and not undergo treatment with surgery, radiation, local ablation, or androgen deprivation. These criteria reflect the current standard of care (11,12) and are as follows:

- PSA doubling time (PSADT) < 3 years
- PSA ≥ 10 ng/mL
- Repeat biopsy
 - $\geq 25\%$ of biopsy tissue cores positive for cancer
 - > 50% of any one biopsy tissue core positive for cancer
 - Men < 70 years at baseline:
 - Gleason sum ≥ 7
 - Men ≥ 70 years at baseline:
 - Gleason sum $\geq 4+3 = 7$

It is recognized that some participants will elect to pursue treatment during the study despite not meeting these criteria for progression. These participants will be censored at the time they begin treatment.

8.7.3 Continuation of the Dietary Intervention

Participants randomized to the dietary intervention arm who progress or elect treatment despite not meeting criteria for progression will continue the intervention for the 2-year duration of the study,

9.0 OUTCOMES ASSESSMENT/QUALITY OF LIFE MEASURES

Seven quality of life measures will be used: Personal Habits Questionnaire, Functional Assessment of Cancer Therapy Scale-Prostate (FACT-P); Memorial Anxiety Scale for Prostate Cancer (Max-PC); International Prostate Symptom Score (IPSS); Expanded Prostate Cancer Index Composite 26 (EPIC-26); Nutrition Self-Efficacy and Satisfaction with the MEAL Program.

9.1 Personal Habits Questionnaire

The personal habits questionnaire, used in the Women's Health Initiative (WHEL) study (66), consists of 8 sets of questions that address a number of generic health behavior questions: cigarette smoking; alcohol consumption; weight change during adult life; adherence to any kind of special diet (e.g. low-calorie, low-fat, low-cholesterol, low salt, high-fiber); recreational physical activity, including mild, moderate and strenuous activity; and physical activity at various ages. These questions, which will be used mainly to make sure randomization produced comparable groups, are as appropriate for men as for women.

9.2 Functional Assessment of Cancer Therapy Scale-Prostate [FACT-P]

The FACT-P [version 4.0], developed by Cella and colleagues (44, 51) is a prostate cancer specific quality of life questionnaire which includes a 27 item 'core' quality of life measure [FACT-G] grouped into four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. There are an additional 12 items specific to prostate cancer, 10 of which are prostate cancer-specific physical problems. Almost all FACT-P subscale items are rated on a 5 item Likert scale, from 0, 'not at all' to 4, 'very much'. The FACT-G has been tested on 630 patients with mixed cancer diagnoses. The internal consistency of the subscales ranges from .65-.82, with excellent internal consistency of the total score: an alpha coefficient of .89. Test-retest reliability is excellent within a 7 day period, with correlations ranging from .82-.92. Convergent validity has been demonstrated, with the FACT correlating significantly with other quality of life measures (FLIC, $r=.79$), and related constructs of psychological distress (e.g. Brief POMS, $r=-.68$) and the ECOG performance rating ($r=-.52$). The FACT-G has been able to distinguish between patients with metastatic and non-metastatic disease. Internal consistency of the Prostate-Specific Concerns subscale was of moderate strength (alpha coefficients ranging from .65-.69) when tested with 130 prostate cancer patients (44). Evidence of convergent validity of the Prostate-Specific Concerns subscale was provided by its significant negative correlations with depression (Inventory to Diagnose Depression, $r=-.34$, $p<.001$), and anxiety (Spielberger Trait Anxiety Scale, $r=-.33$, $p<.001$). Further, significantly greater Prostate-Specific Concerns scores were found for those with more advanced disease than those with earlier stage disease. Sensitivity to change over time was also demonstrated by significantly greater worsening of Physical and Functional Well-being, and Prostate-Specific Concerns subscale scores over a two month period for those with worsening Performance Status (44).

9.3 Memorial Anxiety Scale for Prostate Cancer [MAX-PC]

The Memorial Anxiety Scale for Prostate Cancer [MAX-PC] is a prostate cancer-specific measure to assess patient anxiety due to prostate cancer, PSA tests and fears of recurrence (45, 46). It consists of 18 items: 11 items that parallel items from the Impact of Event Scale, including avoidant and intrusive thoughts about prostate cancer (48); 3 items specific to PSA tests, and 4 items concerning fear of recurrence. The items are grouped into three subscales: Prostate Cancer Anxiety (PCA), PSA Anxiety, and Fear of Recurrence. Fourteen items are rated on a four point Likert scale ranging from 'not at all' to 'often' and 4 items are rated on a Likert scale ranging from 'strongly agree' to 'strongly disagree'. Internal consistency for the total score is excellent (alpha coefficient = .89). The PCA and Fear of Recurrence also demonstrated strong internal consistency (PCA alpha coefficient = .90; Fear = .85) (45). Test-retest reliability is excellent for the total score and three subscales (.74 - .89). The three factor model was confirmed in a second study of the MAX-PC (46). Total scores correlated significantly with other measures of distress, including the HADS ($r=.52$, $p<.0001$) and the Distress Thermometer ($r=.45$, $p<.0001$). Significant correlations were also found between changes in the MAX-PC score with changes in the HADS total score ($r=.30$, $p<.0001$). Further, there was a significant difference among four PSA change groups (i.e. steady, rising, falling and unstable) for the MAX-PC ($p=.003$), PCA ($p=.045$), and the Fear of Recurrence subscale ($p=.0001$).

Anxiety reduction is a legitimate and robust outcome variable and a potential benefit of the counseling intervention. Moreover, it is likely that the distribution of printed dietary guidelines and intermittent phone calls to monitor diet intake, would potentially diminish anxiety in the control group because it involves more attention than active surveillance patients normally receive as part of clinical care (72).

9.4 International Prostate Symptom Score (IPSS)

This is an 8-item scale, widely used in clinical practice, which measures lower urinary tract symptoms. It includes questions encompassing incomplete bladder emptying, frequent urination, urgency, nocturia, intermittency, weak stream, straining, and quality of life related to urinary symptoms (73).

There are robust data to suggest that prostate cancer patients on active surveillance experience significantly decreased urinary health relative to men without prostate cancer. In a cohort analysis of 6,000 community dwelling older men, we observed that compared to men without prostate cancer, men with prostate cancer on active surveillance (i.e. those who had not undergone treatment) reported a significantly diminished quality of life due to urinary symptoms (74). In addition, several published studies have noted that high vegetable diets and higher serum carotenoid concentration are associated with decreased urinary symptoms (75-77).

9.5 Expanded Prostate Cancer Composite Index 26 (EPIC-26)

This instrument is an abbreviated version of the Expanded Prostate Cancer Composite Index (EPIC). It contains 26 questions focusing on 5 distinct health-related quality of life domains relevant to prostate cancer: urinary incontinence, urinary irritation/obstruction, bowel, sexual and vitality/hormonal. Each domain has function and other subdomains. All of the domains for EPIC-26 are reported using a 0-100 score, with higher scores representing favorable health related quality of life. The EPIC-26 demonstrates robust consistency and validity for measuring these important outcomes related to prostate cancer survivorship (78).

9.6 Nutrition Self-Efficacy Scale

The Nutrition Self-Efficacy scale assesses the degree to which individuals are confident that they can control their nutrition (79). The scale assesses perceived self-efficacy, the confidence in one's ability to meet one's goals, and coping self-efficacy, defined as optimistic beliefs about one's capability to deal with barriers that arise in plans. The scale consists of 5 items rated on a 5 point Likert scale, ranging from 'very confident' to 'not confident at all'. Internal consistency was excellent (alpha coefficient = .87, n= 1,722). Evidence of validity was provided by the Nutritional Efficacy Scale correlating significantly with nutritional behavior ($r = .34$, $p < .01$) (80). Because quality of life or anxiety has not been formally evaluated in an AS population or in the setting of a randomized clinical trial among AS patients, a battery of scores will be assessed as exploratory variables, with scores at each time point and changes in scores over time assessed between the intervention and control groups using student's t-test and linear regression modeling.

9.7 Satisfaction with the MEAL Program

At 24 months, those in the MEAL arm of the study will be asked to complete a series of questions about their satisfaction with the MEAL program. All but one question has been used in WHEL, (Women's Healthy Eating and Living, the prior diet study on which this study is based). The MEAL Satisfaction Questionnaire, developed by Pierce and colleagues, includes 26 items with all items rated on Likert scales, with response categories varying by the type of question. The following areas of satisfaction are assessed: satisfaction with the nutritional plan, counseling calls, the counselor, the time and frequency of the calls, expectations that the diet will help to prevent recurrence and improve their overall health, barriers in attaining the dietary goals, and the difficulty encountered in changing and maintaining their diet. Internal consistency meets acceptable standards for the satisfaction with their food intake for the different types of food (5 questions, alpha coefficient = .71), satisfaction with the counselor (9 items, alpha coefficient = .87), and near an acceptable standard for the 2 items assessing how enjoyable and important the counseling calls have been (alpha coefficient = .69). A briefer version of the Satisfaction Questionnaire, to include 23 items, will be used to assess satisfaction with the program for those in the control group. Items concerning counseling and evaluation of the counselor will be eliminated in this questionnaire for the control group participants.

10.0 CORRELATIVE SCIENCE

10.1 Carotenoid Analysis

Carotenoids are organic, plant-based pigments. One of the most common carotenoids is lycopene. Lycopene is an antioxidant and free radical scavenger commonly found in tomatoes. Increased lycopene and tomato intake have been associated with decreased prostate cancer risk. An analysis of the Health Professionals Cohort observed a 21% lower prostate cancer incidence among those with the highest compared to the lowest lycopene intakes. Moreover, those with the highest frequencies of tomato and tomato-based product intake had up to a 35% risk reduction compared to those with the lowest intake (20). In a meta-analysis of 21 published studies, Etminan and colleagues observed that participants with the highest intake (fifth quintile of intake) of raw tomatoes [Relative Risk (RR) 0.89, 95% CI 0.8 to 1.0] or cooked tomatoes (RR 0.81, 95% CI 0.71 to 0.92) had a modest reduction in prostate cancer risk (10). These investigators also noted that while lycopene consumption was not associated with prostate cancer risk (RR 0.99, 95% CI 0.93-1.06), higher serum lycopene concentrations were associated with decreased risk (RR 0.85, 95% CI 0.75-0.97) (81).

Interest in the potential therapeutic benefits of lycopene and/or tomatoes has led to a small number of clinical trials that have produced promising, yet preliminary, results. Stacewicz-Sapuntzakis and Bowen placed 32 patients with prostate cancer on tomato paste-rich diet, 3 weeks before their scheduled prostatectomy. The

patients consumed 26.8 mg of lycopene per day, compared with their usual mean intake of 5 mg/day. These investigators noted significant reductions in serum PSA concentrations and increases in apoptotic index in the intervention group compared with the controls (82). Similarly, Kucuk and colleagues randomized 26 patients with newly diagnosed prostate cancer to receive tomato oleoresin extract containing 30 mg of lycopene or no supplementation for 3 weeks before radical prostatectomy. When compared with the intervention group was found to have smaller tumors, less involvement of surgical margins, and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (83). Chen and colleagues observed in a radical prostatectomy model that men who consumed large amounts of tomato products prior to surgery had less oxidative damage in the prostate (30), while Barber and colleagues noted decreased PSA velocities in men with prostate cancer treated with lycopene supplementation (25).

While these data are compelling, associations of carotenoids with prostate cancer remain unclear. In the MEAL pilot study, there was no significant association of plasma lycopene or other carotenoids with plasma PSA over a 6-month period for AS patients or patients with PSA-only recurrence following surgery or radiation (40-42).

10.2 Polymorphism Analysis

Multiple genetic variants have been identified which are linked to increase risk of developing prostate carcinoma (84-89). There is increasing evidence that genetic factors could not only predispose men to prostate cancer in general but specifically for aggressive disease. For example CASP8 and MDM2 contain variants associated with risk of aggressive prostate carcinoma (90, 91). Cheng et al (92) and Beebe-Dimmer et al (93) demonstrated that at least some 8q24 variants are associated with risk of advanced disease. Duggan et al identified rs1571801, located in the DAB2IP gene, as a candidate which was associated with aggressive PCa in both European-Americans ($p=0.004$) and African-Americans ($p=0.02$) (94). Mononen et al found that 5' untranslated variant in CYP17A1 was associated with an increased risk of high grade PCa (95).

Identification of a population of patients at risk for aggressive disease is only useful if the disease can be prevented or treated effectively. Dietary manipulation holds promise as a way of preventing or ameliorating the risk of developing prostate carcinoma. There is a growing body of evidence that dietary factors may modify genetic risk. Several genes, such as *MnSOD*, *XRCC1*, and *GST*, may modify the association of specific nutrients and foods with prostate cancer risk and groups have called for further research to confirm these initial observations (96). For example, evidence from the Physicians Health Study suggests that manganese superoxide dismutase (*MnSOD*) polymorphism V16A may interact with selenium levels to modify risk of clinically aggressive PCa (97). *MnSOD* genotype were not associated with increased risk of disease. However, when they stratified the cases by prediagnostic selenium levels they found that the cohort with the highest selenium levels and AA genotype were protected against prostate cancer in general and clinically aggressive prostate cancer specifically. Another example of genotype environment interaction is vitamin D and Vitamin D Receptor polymorphisms. A study from the Physicians Health Study demonstrated that while the Vitamin D Receptor polymorphism *BsmI* or *FokI* were not associated with prostate carcinoma, men with *FokI*ff genotype and low vitamin D levels had the highest risk of developing PCa in general and aggressive disease specifically (98). Given that vitamin D oral formulations have been explored as a treatment option for PCa (99), identification of an interaction between genotype and environment could have potential clinical application.

The MEAL study offers the ideal population to study the interaction between genetic risk and diet. First and foremost, if genetic risk is associated with aggressive disease, then patients with the high risk genetic background should be more likely to progress. What is unique about the MEAL study is to determine if dietary modification alters that genetic risk. If it does then genetically high risk patients could modify their diet at the time of diagnosis or possibly sooner. Alternatively, if

diet does not modify risk of progression then more aggressive management could be instituted.

10.3 Correlative Objectives

- 10.3.1** To compare plasma carotenoid concentrations in AS patients receiving dietary intervention compared to no intervention.
- 10.3.2** To correlate plasma carotenoid concentrations with PSADT in AS patients.
- 10.3.3** To correlate plasma carotenoid concentrations with time to pathological progression in AS patients.
- 10.3.4** To compare MnSOD, XRCC1, and GST gene polymorphisms to PSADT in AS patients receiving dietary intervention versus no intervention.
- 10.3.5** To compare MnSOD, XRCC1, and GST gene polymorphisms to time to pathological progression in AS patients receiving dietary intervention versus no intervention.

10.4 Methods

PSA analysis will be conducted at the site from which the patient was recruited. The blood nutrient analysis will take place at UCSD under the direction of Dr. Rock. The carotenoid analysis will be done at UCSD. Plasma carotenoids will be separated and quantified using the HPLC methodology that we have used previously (40, 67, 68), with modifications to reduce oxidative loss and improve recovery of compounds during analysis. Standard reference materials from the manufacturer will be used to validate analytical precision of these procedures. At UCSD, samples will be stored at all times at -70° C or lower temperatures in freezers equipped with temperature alarms in the Moores UCSD Cancer Center that are under the direct supervision of Dr. Rock.

Carotenoid analysis can be evaluated on plasma or serum. Therefore, in addition to the plasma sample, we will be collecting and banking serum for evaluation of carotenoids, if needed, as well as for the evaluation of other circulating markers of interest. A whole blood sample is being collected for DNA isolation and evaluation of genetic polymorphisms that affect antioxidant metabolism such as MnSOD. In addition, there is evidence of other interactions between antioxidant systems and dietary practice. Some of these could have an impact on the prostate such as catechol-o-methyl transferase and glutathione peroxidase.

11.0 STATISTICAL CONSIDERATIONS

11.1 Randomization

Patients will be randomized with equal probability to receive the dietary intervention (experimental arm) or dietary information (control arm). A total of 464 patients will be enrolled to this trial, 232 patients per arm. The study will take a total of 5 years: about 3 years of accrual with an expected accrual rate of 15 patients per month, and 2 years of follow-up for each patient.

Stratification factors: Randomization will be stratified by age (< 70 years vs. ≥ 70 years), race (African American vs. Other) and baseline prostate biopsy (0-12 months prior to registration vs. >12-24 months prior to registration).

11.2 Design

Each patient will be followed for 24 months, and PSA will be evaluated every 3 months starting from baseline. Prostate biopsies are taken at baseline, 12 and 24 months.

The primary outcome of interest in this prevention trial is disease progression defined by (a) PSA doubling time (PSADT) < 3 years, (b) PSA > 10 at any time, or (c) Gleason sum on repeat biopsy ≥ 7 for men younger than 70 years and ≥ 4+3 = 7 for men 70 years or older. These criteria are drawn from one of the largest active surveillance studies to date, the Toronto cohort (12). Data from this cohort indicate that approximately 20% of patients on active surveillance will progress by these criteria: 14% by PSA doubling time and 8%-10% by Gleason score.

Thus, using the log-rank test with a two-sided $\alpha = 5\%$, a sample size of 418 will provide 80% power to detect a difference in progression rate (PGR) of 20% in the control and 10% in the experimental arm during 24 months of follow-up. Under the exponential distributions for the time to progression, the 2-year PGR of 20% vs. 10% corresponds to a hazard ratio (HR) of 2.118. Assuming 10% of dropout rate (including patients who are treated before progression), a total of 464 patients will be enrolled to this trial.

Centralized pathology review will be conducted on the tissue specimens of the first 50 patients. From an analysis of grading by community vs. Johns Hopkins pathologists, Gleason grading of adenocarcinoma in prostate needle biopsy tissue (106), Gleason score was changed from 3+4 by community review to 4+3 by Johns Hopkins review for about 14% of men and from 6 or below to 7 or above for about 8% of men. Assuming about 30% of men in this study will be >70 years old and these two types of changes occur uniformly over the whole range of age, we believe that no more than 10% of men will become ineligible for the study by the centralized pathology review. We will consider increasing the sample size by a maximum of 10% depending on the proportion of men who become ineligible by central pathology review.

11.3 Analysis

The proportion of men who become ineligible by central pathology review will be estimated for each arm. The primary analysis will be done using data from eligible subjects, especially using Gleason scores from central review. However, all statistical analyses will be conducted for the data sets from eligible patients only, as well as all patients randomized in the sensitivity analysis.

Progression: PSADT will be calculated as \log_2 divided by the slope (the least squares estimator) of \log (PSA) observations over time using the last three PSA measurements at months 0, 3 and 6 (100,101). In order to avoid any miscalculation, the PSADT will be calculated at the CALGB Statistical Center, not by each individual site.

Time to progression data will be analyzed using the log-rank test for univariable analysis and the Cox's proportional hazards regression for multivariable analysis adjusting for the stratification factors and other prognostic factors. For the patients who proceed to treatment with surgery, radiation, local ablative therapy or hormonal

therapy before progression within the 2-year follow-up period, the progression time will be censored at the time of withdrawal for treatment.

A recent study in a similar cohort of men undergoing active surveillance (102) reported that PSA kinetics was not closely associated with progression on subsequent surveillance biopsies. In order to address this issue, as a secondary analysis, we will also compare time to progression defined only by Gleason sum on repeat biopsy ≥ 7 for men younger than 70 years and $\geq 4+3 = 7$ for men 70 years or older. Because of decreased number of events, the log-rank test using this definition of time to progression may not have enough power. For example, if the 2-year PGR for the control arm is only 10% by this new definition, then the log-rank test will have only 50% of power with 418 eligible patients with events or full 2 years of follow-up.

Time to Treatment: Probability to proceed to treatment within 2 years (binary observation) and time to treatment (censored time to an event observation) will be analyzed using the chi-squared test and the log-rank test, respectively. We expect that the control arm will have more patients receiving treatment and shorter time to treatment than the experimental arm because of anxiety.

QOL: Quality of life (anxiety and depression, prostate cancer symptom checklist) will be compared between the two arms. The time trajectory of QOL will be estimated using the generalized estimating equation method based on working independent correlation structure (103) and the slope of the time trajectory will be compared between the two arms (104). We will consider taking a log-transformation of QOL observations if it improves the linearity of the time trajectory of QOL. The significance of the two arm comparisons will be adjusted for multiple testing among different QOL subscales using the methodology of Bang, Jung and George (105).

Dietary Recall: Diets will be evaluated at baseline and at 12 and 24 months by a series of three separate 24-hour dietary recalls collected interactively via telephone interview. The increase (from baseline) in mean daily intakes of total vegetables, crucifers, tomato products, beans/legumes and fat will be compared between arms using a two-sample t-test at 12 and 24 months. We may consider transforming (e.g. using logarithm) the data to improve normality of the distributions and variance stabilization. Data will be catalogued and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition Coordinating Center, University of Minnesota).

Correlative Objectives:

(1) Plasma carotenoid concentrations (PCC) will be compared between the two arms using a two-sample t-test. A log-transformation of the PCC observations may be considered in order to improve the normality of the distributions and variance stabilization.

(2) PCC will be correlated with PSADT for the patients. Descriptive analysis using scatter plots and regression analysis will be conducted. Intervention and known predictors including the stratification factors will be adjusted in multivariable analysis.

(3) Time to pathological progression (i.e., Gleason sum on repeat biopsy ≥ 7 for men younger than 70 years and $\geq 4+3 = 7$ for men 70 years or older) will be regressed on PCC in AS patients using Cox's regression method. Intervention and known predictors including the stratification factors will be adjusted in multivariable analysis.

(4) The expression level of MnSOD, XRCC1 and GST will be correlated with PSADT within each arm. The expression level of these genes may be highly correlated with PSADT in the control arm. However, if dietary modification alters the genetic risk, the association may be insignificant or less significant in the experimental arm.

(5) The expression level of MnSOD, XRCC1 and GST will be correlated with time to pathological progression using Cox regression method within each arm. The expression level of these genes may be highly correlated with time to pathological

progression in the control arm. However, if dietary modification alters the genetic risk, the association may be insignificant or less significant in the experimental arm.

11.4 Interim Analysis

11.4.1 Primary Endpoint

At each interim analysis, superiority and futility tests on PFS will be conducted as follows.

Superiority: A superiority test is to test if the experimental arm has a longer PFS than the control arm. The first interim analysis for superiority will be conducted when 80 patients progress or complete the 2 years of follow-up. With 6 months of run-in period and a monthly accrual of 15 patients, this will occur at approximately 33 months. After this time, interim analyses will be conducted every six months corresponding with scheduled meetings of the CALGB Data and Safety Monitoring Board (DSMB). The final analysis will be conducted 2 years after the completion of accrual. With the expected study plan, there should be about 4 or 5 interim analyses before the final analysis. The superiority testing during the interim analyses will be using one sided $\alpha=0.0025$. The final analysis will be using one-sided $\alpha=0.025$. Due to the relatively small number of interim analyses and the small alpha spending at each interim analysis, the overall type I error rate will not be much larger than the nominal one-sided $\alpha=0.025$ (107).

Futility: Futility testing will be conducted at the time of each interim analysis for superiority. The futility statistics calculated for $H_0:HR \geq 2.118$ vs. $H_1:HR < 2.118$ will be compared with the critical values with 1-sided $\alpha=0.005$ at each interim analysis. The futility rule has about 84% probability to reject the experimental arm during the interim analyses when the two arms have similar PFS (i.e. $HR=1$).

11.4.2 Progression Rate

The power of the log-rank test depends on the PGR in the two arms. An interim analysis will be conducted when 400 patients are enrolled on the study to check if the specified 20% of 2-year PGR is accurate or not. At the interim analysis, the 2-year PGR of the control arm will be estimated. If the estimate is smaller than 20%, we will recalculate the sample size using the estimated 2-year PGR for the control arm, $HR=0.472$, two sided $\alpha=0.05$ and a power of 80% and consider increasing the sample size by a maximum of 20% of the current sample size. For example, if the estimated 2-year PGR for the control arm is 18%, then we need 466 eligible patients (about 11% increase from 418 eligible patients). In case the observed progression rate is so low that a maximum of 20% increase in sample size does not guarantee a reasonable power for the primary endpoint, we will consider suspending the study for revision.

11.4.3 Accrual Monitoring

The accrual rate will be monitored by DSMB complying with CTEP's Early Stopping Guidelines for Slow Accruing Trials.

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13.0 MODEL CONSENT FORM**The Men's Eating and Living (MEAL) Study: A Randomized Trial of Diet to Alter Disease Progression in Prostate Cancer Patients on Active Surveillance**

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation. [Attach NCI booklet "Taking Part in Clinical Trials: What Cancer Patients Need to Know"]

You are being asked to take part in this study because you have been diagnosed with prostate cancer and are receiving regular follow-up care with your primary physician.

Why is this study being done?

You are being asked to take part in a research study of men who are undergoing active surveillance for their prostate cancer. The purpose of the study is to find out more about how diet may prevent prostate cancer from getting worse.

How many people will take part in this study?

About 464 men will participate in this study.

What will happen if I take part in this research study?**Before you begin the study . . .**

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A complete history and physical exam including a digital rectal exam
- A PSA test

After you are enrolled in the study, you will be asked to complete a questionnaire about your personal habits and provide about 6 teaspoons of blood for research. Study researchers will analyze the blood to determine carotenoid and cholesterol levels. Carotenoid refers to the red to yellow pigments responsible for the color of many plant organs or fruits, such as tomatoes or carrots. Cholesterol is a fat-like substance that is made by the body and is found naturally in animal foods such as meat, fish, poultry, eggs, and dairy products. The blood samples will be used for research purposes only, and will not replace your usual medical care. Your carotenoid, and cholesterol levels as measured in this study will not be reported to you or your doctor.

During a two-week period after enrollment, study researchers will call you on three different days over the telephone and ask you questions about your medical history and diet. During these interviews, called “24-hour dietary recalls,” you will be asked to recall everything you ate and drank during the previous 24 hours. You may skip any question that makes you uncomfortable. These telephone interviews will take approximately 20 minutes.

During the study . . .

If you are able to complete the three 24-hour dietary recall interviews and you choose to participate in the study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

Group 1

If you are in Group 1 (often called "Arm A") you will be assigned to a program providing you with telephone counseling to help change your diet. You will be asked to change your diet to increase the amounts of fiber-rich plant foods (vegetables, fruit, whole grains, and beans) that you eat. You will receive counseling assistance to help you achieve the dietary goals. These counseling calls will take an average of 30 minutes and will occur twice weekly for the first two weeks, and gradually decrease in frequency (weekly, bi-monthly, monthly). The counseling calls may be monitored and audio-taped for quality assurance purposes. After the first six months, your telephone counselor will call you periodically throughout the remainder of the study to check on how you are maintaining the study diet. You will receive a total of 22 calls over the 24-month period. Regularly scheduled newsletters will also be provided to you by mail.

Group 2

If you are in Group 2 (often called "Arm B") you will be assigned to a program providing you with information about diet and cancer. You will receive an initial orientation telephone call that will take about 5 to 10 minutes as well as a booklet containing USDA Dietary Guidelines for Americans. Regularly scheduled newsletters will also be provided to you by mail.

Tests and Procedures

Participants in groups 1 and 2 will complete the tests and procedures listed below. They are part of regular cancer care.

- A complete history and physical exam every 3 months
- A PSA test every 3 months
- A digital rectal examination every 12 months at the urologists discretion
- A prostate biopsy every 12 months

You will also be asked to do the following while you are on the study:

- Every 6 months you will be asked to complete questionnaires about your current health, your food preparation and eating habits, your usual food intake over the past year, your quality of life, function and anxiety.
- Participate in 24-hour dietary recall interviews 12 and 24 months after you start the study. There will be three interviews at each of these times. Each set of these recalls will happen on 3 separate days during a scheduled 3-week period. You may skip any question that makes you uncomfortable.
- Provide about 6 teaspoons of blood 12 and 24 months after you start the study. These blood draws will normally be scheduled early in the morning and you must agree to eat and drink nothing but water and your normal medications for 6 hours prior to the blood collection.

	Month							
	3	6	9	12	15	18	21	24
Clinic Visit*	X	X	X	X	X	X	X	X
Diet Recall				X				X
Questionnaires by Phone		X		X		X		X
Research Blood				X				X
Prostate Biopsy				X				X
Telephone Counseling	For patients in Group 1 only: 22 telephone calls over 2 years							

* Includes history and physical, height, weight, PSA test and a digital rectal examination every 12 months at the urologists discretion.

When I am finished

After you have completed the study, you will continue with your usual cancer care.

How long will I be in the study?

You will be in the study for 2 years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor or nurse if you are thinking about stopping or decide to stop.

It is important to tell your study doctor if you are thinking about stopping so you can discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. You should talk to your study doctor about any side effects that you have while taking part in the study.

Possible risks from changing your diet

- Your skin, especially on the palms of your hands and the soles of your feet, may become yellow because of a diet high in carotenoids.
- You may become bloated or have a lot of gas for a short period because you may be eating more vegetables and dietary fiber than usual. You may get diarrhea or become constipated at first, but only until your body can adjust to your new diet.

Other risks

- There may be a small risk in the process of drawing blood. You may faint or become dizzy. You may feel a little pain or discomfort as the needle goes through the skin. Some bleeding or bruising may occur at the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent this. Very rarely, your arm may swell or become infected.

Are there benefits to taking part in the study?

There will be no direct benefits to you other than those associated with changing your diet. The investigators may learn more about how diet plays a role in changing the way prostate cancer can spread in the body. This information could help future prostate cancer patients.

It is important to remember that while there may be benefits, you should continue to be followed by your doctor for your prostate cancer.

What other choices do I have if I do not take part in this study?

You may choose not to take part in this study. If you do not take part in the study, you should discuss with your doctor the appropriate treatment or surveillance plan for your prostate cancer. Those who choose not to participate in this study will continue under the care of their doctors for prostate cancer. You may also choose to take part in another research study.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical record for research, quality assurance, and data analysis include:

- Cancer and Leukemia Group B (CALGB)
- National Cancer Institute
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials, may also view your records if you are participating in this trial through one of their institutions.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will be responsible for the charges related to your cancer care. All study measurements and materials directly related to the research will be provided to you free of charge.

You will be responsible for the cost of the food specified by the study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [http://cancer.gov/clinical trials/understanding/insurance-coverage](http://cancer.gov/clinical_trials/understanding/insurance-coverage). You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor _____ if you feel that you have been injured because you took part in this study. You can tell the doctor in person or call him at _____.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from your institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data and Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

It may be necessary to contact you at a future date regarding new information about the intervention you have received. For this reason, we ask that you notify the institution where you participated in the study of any changes in address. If you move, please provide your new address to:

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ at _____.

For questions about your rights while taking part in this study, call the _____ Institutional Review Board (a group of people who review the research to protect your rights) at _____.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: [http://cancer.gov/clinical trials/](http://cancer.gov/clinical%20trials/)
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in the study.

Participant _____ Date _____

Participant Name (please print) _____

APPENDIX I

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

To submit site registration documents:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-888-823-5923
Fax: 215-569-0206
Email:
CTSURegulatory@ctsu.coccg.org

For patient enrollments:

CTSU Data Operations Center
Phone: 1-888-462-3009
Fax: 1-888-691-8039
Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)
[Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 AM and 5:30 PM.]

Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:

CALGB Statistical Center
Hock Plaza
2424 Erwin Road, Suite 802
Durham, NC 27705
Tel: 919-668-9350
Data Operations Fax: 919-668-9348
Teleform Fax: 919-416-4990

Sites should submit Teleforms via Fax or Mail. See Section 6.0 Data Submission Section for details on forms submission.

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment related questions: Contact the CALGB Study Chair.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org. To access the members' section of the Web site, enter your IAM-CTEP user id and password where indicated.

Requirements for CALGB-70807 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- Notification of site approval and randomization assignment by CALGB. (CALGB will send notification to the CTSU Regulatory Office.)

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the members' section of the CTSU Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

All forms and documents associated with this study can be downloaded from the CALGB 70807 Web page on the members' section of the CTSU member Web site (<https://www.ctsuo.org> –enter user id and password where indicated). Patients can be registered only after: 1) the site is assessed and randomized by CALGB, 2) site registration documents are on file with the CTSU Regulatory Office and the study site is listed as 'approved' in the CTSU RSS, 3) patient pre-registration has been successfully completed, and 4) all patient eligibility criteria have been met.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the members' section of the CTSU web site at <http://www.ctsuo.org>.

In addition to participating in CALGB-70807, sites may also register patients to a treatment trial following the parameters set forth in Section 4.0.

CTSU PROCEDURES FOR PATIENT ENROLLMENT

Pre-Registration

Prior to being enrolled into this study, patients must:

1. Confirm eligibility criteria per section 4.0.
2. Sign and date all applicable consents and authorization forms.
3. Complete the following forms (available from the CALGB 70807 Web page on the members' section of the CTSU members' Web site (<https://www.ctsuo.org> – enter user id and password where indicated)):

- **Pre-Registration Worksheet**

- **CTSU Patient Enrollment Transmittal Form**

Fax these forms to the CTSU Registrars at 1-888-691-8039 between the hours of 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays); however, please be aware that registrations received after 5:00 PM will be processed the next day. Registration is limited to operating hours of the CALGB Registration office (9AM-5PM ET). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.

When the patient is preregistered, a patient identification number will be generated, which will be kept in the records. The CTSU registrar will confirm registration by fax.

- **MEAL Contact Information Form C-2010**

Within 24 hours of pre-registration, sites must fax the MEAL Contact Information Form C-2010 to Vicky Newman at 858-822-6896, and also notify Vicky Newman via email at vinewman@ucsd.edu.

Within one week of receiving the MEAL Contact Information Form from sites, the nutrition unit at UCSD will call patients on randomly selected days to complete three 24-hour dietary recalls. The series of dietary recalls will be completed within 2-3 weeks.

Run-In

After pre-registration, the following must be submitted for each patient:

- **Personal Habits Questionnaire** - This form must be submitted within 2 weeks to the CALGB statistical center (per Section 6.1).

- **Baseline 6-hour fasting blood samples** - must be provided per instructions in protocol Section 6.2.

Participants will have two chances to successfully complete the run-in. Upon completion of the run-in, UCSD will notify the site and the statistical center about patient eligibility. Eligible patients who completed the run-in and submitted a blood sample will then be registered per CTSU Procedures outlined below.

Registration

Prestudy requirements for patient enrollment on CALGB-70807:

- Patient must successfully complete pre-registration run-in (sample collection and diet recall).
- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- Once the above criteria have been met, the following steps should be taken:
 1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Monday-Friday. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
 2. Complete the following forms:
 - Registration Worksheet
 - CTSU Patient Enrollment Transmittal Form
 3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. Registration is limited to the operating hours of the CALGB Registration Office (9 am – 5 pm ET). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
 4. After registration is complete, the patient can be randomized according to the stratification factors which must be entered to obtain a treatment assignment.
 5. The CTSU registrar will confirm registration by fax including the treatment assignment for the enrolling site.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the CALGB-70807 Web page located on the members' section of the CTSU Web site (<https://www.ctsuo.org> – enter user id and password where indicated). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the CALGB [see Section 6.0] unless an alternate location is specified in the protocol. Do not send study data to the CTSU. A completed CTSU-CALGB coversheet should accompany all data submissions.
3. The CALGB Statistical Center will send (generally via email but may be sent via postal mail or fax) query notices and delinquency reports directly to the site for reconciliation. Please

send query responses and delinquent data to the CALGB Statistical Center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must maintain current CTEP IAM account contact information**. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

SPECIAL MATERIALS

1. Special materials, including the Participant Notebook and the USDA Dietary Guidelines for Americans, will be provided by CALGB.
2. UCSD staff will provide 8 regularly scheduled newsletters to participants on both arms of the study over the course of 24 months as outlined in Section 8.3.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group. The audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be funded by the CTSU but issued by the credited Group.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page <http://ctep.cancer.gov/monitoring/guidelines.html>.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.

Appendix 2

Parsons JK, Pierce JP, and Marshall J. The Men's Eating and Living (MEAL) Study: a randomized trial of diet to alter disease progression in prostate cancer patients on active surveillance. Presented at the Department of Defense Innovative Minds in Prostate Cancer Meeting; March 2011; Orlando, FL

Background and objectives

There is widespread interest among physicians and patients in utilizing diet for the prevention and treatment of prostate cancer. Despite robust epidemiological and pre-clinical data suggesting that dietary modifications may alter prostate cancer initiation and progression, however, there remains a dearth of clinical trials. We will study the effect of a vegetable-intense diet on disease progression in prostate cancer patients on active surveillance.

Brief description of methodologies

The Men's Eating and Living (MEAL) study is a randomized, Phase III clinical trial designed to test the effect of diet intervention on disease progression in prostate cancer patients on active surveillance. This multicenter national trial is being run through Cancer and Leukemia Group B (CALGB) and the National Cancer Institute (NCI). The primary outcome is disease progression defined by total PSA, PSA doubling time, and pathology (Gleason sum and tumor volume) on repeat prostate biopsy. Participants are considered to have reached study endpoint if they progress by any one of these criteria. Secondary outcomes include treatment seeking, anxiety, and quality of life.

The diet intervention is a unique, validated, telephone-based communication and counseling system designed to promote vegetable intake in prostate cancer patients. We previously demonstrated the efficacy of this intervention for effecting diet change in a randomized clinical trial of 74 patients. An important nuance of diet intervention trials is that participants may be inclined to exaggerate their compliance with diet goals on questionnaires. Thus, we will measure serum carotenoid concentrations—an objective biomarker of vegetable intake—to independently verify diet composition.

In prior cohort studies of active surveillance patients, 2-year progression varied from 20% to 35%. Using the log-rank test with a two-sided $\alpha = 5\%$, a sample size of 418 will provide 80% power to detect a difference in progression rate (PGR) of 20% in the control and 10% in the experimental arm during 24 months of follow-up. Under the exponential distributions for the time to progression, the 2-year PGR of 20% vs. 10% corresponds to a hazard ratio (HR) of 0.472. Assuming a 10% dropout rate (including patients who are treated before progression), a total of 464 patients will be enrolled to this trial.

Results to date

We hypothesize that our intervention will decrease disease progression, decrease the incidence of active treatment, diminish anxiety, and improve quality of life for prostate cancer patients on active surveillance.

Conclusions

The MEAL study is the first large, multi-center, randomized clinical trial of diet for the treatment of prostate cancer and the first major, federally funded study of an intervention targeted for active surveillance patients.

Appendix 3

**A Randomized Trial of Diet in Men with Early Stage Prostate Cancer:
Rationale and Design of the Men's Eating and Living (MEAL) Study
(CALGB 70807)**

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Abstract

Background: Diet may substantially alter prostate cancer initiation and progression.

However, large-scale clinical trials of diet modification have yet to be performed for prostate cancer. The Men's Eating and Living (MEAL) Study (CALGB 70807) is investigating the effect of increased vegetable consumption on clinical progression in men with localized prostate cancer.

Study Design: MEAL is a randomized, Phase III clinical trial designed to test whether an intervention that increases vegetable intake will decrease the incidence of clinical progression in men with clinically localized prostate cancer on active surveillance. We are randomizing 464 patients to either a validated telephone-based diet counseling intervention or a control condition in which patients receive a published diet guideline. The intervention will continue for two years. The primary outcome variable is clinical progression defined by serum prostate-specific antigen (PSA) and pathological findings on follow-up prostate biopsy. Secondary outcome variables include incidence of surgical and non-surgical treatments for prostate cancer, prostate-cancer related patient anxiety and health-related quality of life.

Conclusion: The MEAL Study is assessing the effectiveness of a high-vegetable diet intervention for preventing clinical progression in men with localized prostate cancer on active surveillance.

Introduction

Due to widespread prostate-specific antigen (PSA) screening, approximately 50% of men diagnosed with prostate cancer present with relatively indolent disease.^{1,2} Many of these patients nevertheless undergo surgery, radiation, or other aggressive treatments associated with chronic—and substantial—side effects.³⁻⁵ Active surveillance, which entails careful monitoring of selected patients with early stage prostate cancer and treatment of those who demonstrate evidence of disease progression, provides a viable and safe alternative to immediate treatment.⁶⁻⁸ However, approximately 30% to 35% of patients pursuing active surveillance will clinically progress and undergo aggressive treatment with surgery or radiation within 5 years, while others will opt for treatment even though they do not meet the objective criteria for progression.⁷⁻⁹

A novel strategy of potentially decreasing the number of active surveillance patients who require aggressive treatment is diet modification. Diet may substantially influence prostate cancer initiation and progression,¹⁰⁻¹² and altering dietary intake—specifically, switching to a diet that emphasizes vegetable intake and de-emphasizes meat and fat intake—might decrease the risk of clinical progression.^{10,13} Prostate cell line and animal studies demonstrate that components of cruciferous vegetables (isothiocyanates) and tomatoes (lycopene) induce apoptosis of prostate cancer cells, inhibit carcinogenesis, and promote the expression of cytoprotective enzymes in prostate tissue.¹⁴⁻¹⁶

Clinical evidence supporting these epidemiological and laboratory data, however, are limited. Three small trials have evaluated diet change as a therapy for prostate

cancer,¹⁷⁻¹⁹ one of which¹⁸ suggested a beneficial effect in active surveillance patients who implemented extreme lifestyle changes.

We designed and successfully pilot tested a telephone-based diet intervention for prostate cancer patients based on well-established principles of social cognitive theory. This intervention produced robust diet changes and led to increased plasma carotenoids—a biomarker for vegetable intake—in prostate cancer patients, including those on active surveillance.^{20,21} The Men's Eating and Living (MEAL) Study is designed to assess the efficacy of this intervention to prevent clinical progression in men with localized prostate cancer on active surveillance

Research Design and Methods

Eligibility and exclusion criteria

Eligible patients are 50 to 80 years of age with biopsy-proven adenocarcinoma of the prostate who were diagnosed within 24 months prior to presentation, had ≥ 10 biopsy tissue cores procured, had $< 25\%$ of biopsy tissue cores positive for cancer, had $\leq 50\%$ of any single biopsy tissue core positive for cancer and chose to pursue active surveillance. Other eligibility criteria include biopsy Gleason sum ≤ 6 for men ≤ 70 years; biopsy Gleason sum $\leq (3 + 4) = 7$ for men > 70 years; clinical stage $\leq T2a$; serum PSA < 10 ng/mL; life expectancy at least 3 years; and the ability to read and comprehend English language text and to understand spoken English over the telephone.

Exclusion criteria include prostate cancer with distant metastases; prior treatment for prostate cancer by surgery, radiation, minimally-invasive local ablation (i.e.

cryosurgery or high-intensity focused ultrasound), or androgen deprivation therapy; current oral anticoagulation therapy with warfarin; a history of non-cutaneous malignancy (other than non-melanoma skin cancer) in the previous 5 years; current consumption of ≥ 6 servings per day of fruits and vegetables (not including juices); unwillingness to adopt a vegetable-rich diet; intolerance of cruciferous vegetables; psychiatric illness precluding compliance with the intervention and/or obtainment of informed consent; and medical conditions which in the opinion of the treating physician would make the protocol unreasonably hazardous.

Patients taking dietary supplements, including lycopene and beta-carotene, are eligible. Patients receiving treatment with the 5-alpha reductase inhibitors finasteride or dutasteride within 90 days are not eligible. Should they wish to enroll, patients will become eligible after discontinuation and then a 90-day washout period. Patients who begin taking these medications while on study will be censored at time of medication initiation.

Study design

The MEAL Study is a randomized, phase III clinical trial. The intervention is a validated, telephone-based counseling program.^{20,22} We are randomizing 464 patients on active surveillance to either the telephone-based counseling intervention or the control condition in which patients receive printed materials from the Prostate Cancer Foundation that recommend consumption of a healthy diet (Figure 1).

Telephone counseling intervention

All counseling is performed by telephone from the Moores UCSD Cancer Center. The telephone counseling protocol follows a step-wise, phased approach that employs strategies adopted from social cognitive theory.²³ Motivational interviewing techniques²⁴ are utilized to help participants assume and maintain responsibility for their own behavior change.

After randomization, each intervention participant is assigned to a personal counselor. Counselors work morning, afternoon, or evening shifts, and every effort is made to assign the participant to a counselor working when he prefers to receive calls.

The dietary targets for the intervention arm are designed to be challenging yet achievable. Men randomized to the intervention diet are encouraged to consume daily at least 7 servings of vegetables (including at least 2 servings of cruciferous vegetables and 2 servings of tomatoes), 2 servings of fruit, 2 servings of whole grains, and 1 serving of legumes. To maximize the intake of potentially beneficial bioactive food components, intervention participants are encouraged to consume “bold” (“big color” and “strong flavor”) vegetables and fruit. In addition to cruciferous vegetables and tomatoes, these foods include dark green leafy vegetables, deep orange vegetables and fruits, allium vegetables (onions, garlic), berries, and citrus fruit. Servings are defined as a half-cup cut up raw or cooked vegetables, fruit, or 100% vegetable juice; one cup raw leafy green vegetable; a half cup cooked whole grain, or legume; 1 slice whole-grain bread. Because of lower content of potentially beneficial bioactive food components, iceberg lettuce, white potatoes, and fruit juices are not counted toward the daily goals.

The telephone counseling intervention is divided into 4 phases over a 24-month period. Telephone calls are scheduled more frequently at the beginning of the intervention when participants need the most support. During the first phase, counseling sessions are focused on setting and achieving short-term goals to build self-efficacy. Each call during this phase starts with a 24-hour recall to monitor dietary intake. Performance is discussed with the participant and positive aspects of achievements highlighted prior to negotiating a new set of sub-goals. To maximize the probability of success, counselors focus on helping participants identify barriers to achieving goals and ensuring that participants take these barriers into consideration when setting their iterative set of short-term goals.

The second phase focuses on consolidation of the new dietary pattern into the daily lifestyle of the participant. Emphasis is placed on goals for establishing an environment that is conducive to achieving the new dietary pattern, such as altering the type of food available in the house, modifying recipes and food preparation, and focusing on appropriate portion sizes, eating patterns, and eating behaviors. In this phase, participants are assisted in developing a global self-assessment of performance rather than relying on a 24-hour recall.

The third phase focuses on relapse prevention. As vulnerability to relapse is known to be associated with a declining self-efficacy,^{[25](#)} the counselor checks self-efficacy at each call and revisits earlier goal setting strategies if needed.

The fourth phase focuses on providing positive feedback on achievements and maintaining participant accountability, and their commitment to their lifestyle changes

and to the study. The counselor continues to monitor self-efficacy and help problem solve barriers that arise.

To ensure intervention fidelity, counselors completed an intensive 80-hour training program that reviews the rationale for the study, protocols for conducting 24-hour recalls, and extensive role-playing using a computerized structured protocol. The intervention focuses on a series of questions, and responses are entered into the study database in real time. A registered dietitian supervises the intervention team and conducts regular performance reviews. Counselors attend a monthly case management meeting, sharing issues and solutions, as well as reviewing recent relevant literature.

Primary outcome

The primary outcome variable of MEAL is clinical progression, defined as PSA > 10 ng/nL, PSA doubling time (PSADT) < 3 years, or any of the following findings on repeat prostate biopsy: > 25% of biopsy tissue cores positive for cancer, > 50% of any biopsy tissue core positive for cancer, Gleason sum ≥ 7 for men ≤ 70 years, or Gleason sum $\geq (4 + 3) = 7$ for men > 70 years.

Secondary outcomes

Secondary outcomes include incidence of surgical and non-surgical treatment in patients whose disease does not meet the definition of clinical progression, anxiety as measured by the Memorial Anxiety Scale for Prostate Cancer (Max-PC), urinary symptoms as measured by the International Prostate Symptom Score (I-PSS), and quality of life (QoL) as measured by the Functional Assessment of Cancer Therapy

Scale-Prostate (FACT-P) and Expanded Prostate Cancer Index Composite 26 (EPIC-26).

Outcome evaluation

Each patient will be followed for 24 months, and PSA is evaluated every 3 months starting from baseline. PSADT will be calculated as \log_2 divided by the slope (the least squares estimator) of \log (PSA) observations over time using the latest 3 PSA measurements at months 0, 3 and 6 (100,101). To ensure comparability, the PSADT will be calculated at the Alliance Statistics and Data Center.

Prostate biopsies are performed within the 24-month period prior to baseline and again 24 months after baseline. Centralized pathology review is conducted on the prostate biopsy tissue cores to assess eligibility and progression. A separate team of telephone assessors evaluate the diets of all study participants at baseline, 12 months, and 24 months by a series of 3 separate 24-hour dietary recalls collected via telephone interview, which uses the Nutrition Data Systems for Research (NDS-R, current version 2010, University of Minnesota Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) software and nutrient database. Fasting blood samples are collected at baseline, 12 months, and 24 months and analyzed for plasma carotenoid concentrations, a biomarker of vegetable and fruit intake, using high-performance liquid chromatography methodology.²²

Statistics

We are randomizing patients 1:1 to receive the dietary intervention (experimental arm) or dietary information (control arm). The log-rank test with a two-sided $\alpha = 5\%$ and a sample size of 418 has 80% power to detect a difference in progression rate of 20% in the control versus 10% in the experimental arm during the 24-month follow-up period. Under the exponential distribution assumption for the time to progression, the 2-year progression rate of 20% versus 10% corresponds to a hazard ratio (HR) of 2.1. Assuming a 10% dropout rate (including patients who are treated before progression), we are enrolling a total of 464 patients. We are stratifying randomization by age (< 70 years versus ≥ 70 years), race (African American versus Other) and baseline prostate biopsy (0-12 months prior to registration versus > 12-24 months prior to registration).

We are comparing time to clinical progression between the two arms using the log-rank test for univariate analysis and Cox's proportional hazards regression for multivariate analysis adjusting for stratification and other prognostic factors. We are censoring the patients who proceed to treatment with surgery, radiation, local ablative therapy or androgen deprivation therapy before progression within the 2-year follow-up period at the time of treatment.

We are also comparing the probability to proceed to treatment within 2 years using the chi-squared test. We are estimating the time trajectory of QoL using the generalized estimating equation method based on working independent correlation structure and comparing the slopes for the two arms of the time trajectory,²⁵ adjusting for multiple testing among different QoL subscales using the methodology of Bang, Jung and George.²⁶

We will compare the changes from baseline in mean daily intakes of total vegetables, crucifers, tomato products, beans/legumes and fat between the two study arms with two-sample t-tests at 12 and 24 months. We will compare the changes in plasma carotenoid concentrations from baseline between the two arms using a two-sample t-test. We will correlate carotenoid concentrations with PSADT, using descriptive analysis with scatter plots and regression analysis, and adjusting intervention and known predictors including the stratification factors in multivariate analysis.

We will consider logarithmic transformations of the data to improve normality of the distributions and variance stabilization as necessary.

Discussion

The MEAL Study is the first large-scale clinical trial of a dietary intervention for prostate cancer. Assessing the therapeutic efficacy of diet requires the accumulation of data from rationally designed trials focused on feasible interventions that do not place undue burdens on patients. The MEAL Study promotes robust diet changes through a telephone counseling system that has previously been shown to effectively promote dietary change in breast cancer survivors.²⁷ The use of a centralized service to conduct the intervention by telephone has a number of strengths that include intervention fidelity and significant economies of scale. The intervention could likely be applied to relatively large patient populations cheaply and efficiently.

Our innovative telephone-based intervention focuses on beneficial dietary components that have been associated with decreased prostate cancer incidence and

progression in observational studies. The intervention is inexpensive enough to be considered a population intervention. The counseling protocol is stepped and utilizes principles of social cognitive theory^{28,29} and motivational interviewing.³⁰ A similar telephone-based counseling program produced prolonged diet changes in breast cancer patients: in a study of over 1,500 breast cancer survivors, those receiving the intervention maintained significantly increased vegetable intakes and plasma carotenoid increases for at least 4 years.³¹

Reducing the number of active surveillance patients who receive treatment represents an important opportunity to minimize treatment-associated morbidity, improve quality of life, and contain health care costs. Diet change represents an innovative approach to treating prostate cancer with the potential to promulgate a novel therapeutic paradigm: dietary management, without curative intent, of early stage prostate cancer.

Moreover, because prostate cancer diagnosis is a source of considerable anxiety and diminished quality of life,³² dietary intervention also may encourage patients without clinical progression to remain on active surveillance rather than choosing treatment. Many patients with no objective PSA or pathologic criteria for progression will nonetheless opt for treatment, presumably due to anxiety associated with their diagnosis.³³ For these patients, diet change potentially provides an intervention or therapy on which to focus, possibly dissuading otherwise lower risk men from pursuing unnecessarily aggressive, morbidity-generating treatments.

In summary, the MEAL Study uses a centralized, telephone-based counseling intervention to assess the effectiveness of a high-vegetable diet for preventing clinical

progression, improving health-related QoL, and decreasing anxiety in men with localized prostate cancer on active surveillance. This study holds the potential to substantively inform the treatment of early stage prostate cancer.

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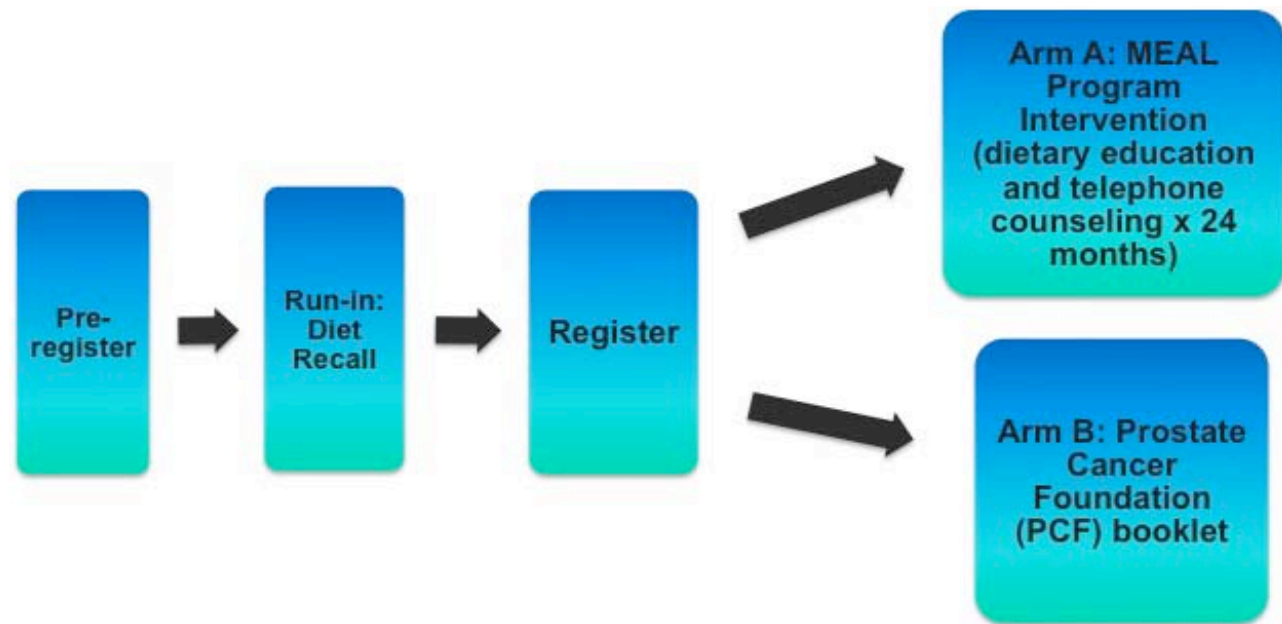
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Figure 1. The Men's Eating and Living (MEAL) Study (CALGB 70807) schema



Appendix 4

A Randomized Pilot Trial of Dietary Modification for the Chemoprevention of Noninvasive Bladder Cancer: The Dietary Intervention in Bladder Cancer Study

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Abstract

Epidemiological data suggest robust associations of high vegetable intake with decreased risks of bladder cancer incidence and mortality, but translational prevention studies have yet to be conducted. We designed and tested a novel intervention to increase vegetable intake in patients with noninvasive bladder cancer. We randomized 48 patients aged 50 to 80 years with biopsy-proven noninvasive (Ta, T1, or *carcinoma in situ*) urothelial cell carcinoma to telephone- and Skype-based dietary counseling or a control condition that provided print materials only. The intervention behavioral goals promoted seven daily vegetable servings, with at least two of these as cruciferous vegetables. Outcome variables were self-reported diet and plasma carotenoid and 24-hour urinary isothiocyanate (ITC) concentrations. We used two-sample *t* tests to assess between-group differences at 6-month follow-up. After 6 months, intervention patients had higher daily intakes of vegetable juice ($P = 0.02$), total vegetables ($P = 0.02$), and cruciferous vegetables ($P = 0.07$); lower daily intakes of energy ($P = 0.007$), fat ($P = 0.002$) and energy from fat ($P = 0.06$); and higher plasma α -carotene concentrations ($P = 0.03$). Self-reported cruciferous vegetable intake correlated with urinary ITC concentrations at baseline ($P < 0.001$) and at 6 months ($P = 0.03$). Although urinary ITC concentrations increased in the intervention group and decreased in the control group, these changes did not attain between-group significance ($P = 0.32$). In patients with noninvasive bladder cancer, our novel intervention induced diet changes associated with protective effects against bladder cancer. These data show the feasibility of implementing therapeutic dietary modifications to prevent recurrent and progressive bladder cancer. *Cancer Prev Res*; 1–8. ©2013 AACR.

Introduction

In the United States in 2012, there were an estimated 73,510 new cases of and 14,480 deaths from bladder cancer (1). The U.S. population prevalence is approximately 600,000 persons and continues to increase annually (2). Bladder cancer is the fourth most frequently diagnosed cancer among men and—due to the high costs of diagnosis, treatment, and posttreatment surveillance—the single most expensive cancer to treat (3). Collectively, these observa-

tions underscore the considerable challenges bladder cancer poses to the public health and highlight an important need to develop innovative, novel therapies for bladder cancer prevention and control.

A potential means of decreasing the morbidity and mortality of bladder cancer is through lifestyle change. Modifiable risk factors present novel, practical targets for primary and tertiary bladder cancer chemoprevention because modulations of these factors potentially exert beneficial, disease-specific health effects. For example, smoking is strongly associated with an increased risk of incident bladder cancer, and a recent cohort analysis of patients with noninvasive bladder cancer observed that longer-term smoking cessation was associated with reduced risks of disease recurrence and progression of 34% and 58%, respectively (4).

Robust epidemiological data indicate beneficial associations of increased vegetable intake, particularly cruciferous vegetables, with decreased risks of incident and progressive bladder cancer (5). In the Health Professional's Follow-Up Study, those in the highest quartile of cruciferous vegetable intake had a 50% reduced risk of urothelial cancer compared to those in the lowest quartile (6). In a cohort of bladder cancer patients, increased consumption of raw

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broccoli was associated with a 43% decreased risk of death from bladder cancer (7). Other population-based studies have observed similar patterns (8, 9).

Translational studies of lifestyle modifications and bladder cancer, however, have yet to be conducted. In a randomized clinical trial, we tested a novel intervention to increase vegetable intake in patients with noninvasive bladder cancer.

Materials and Methods

Study population

We recruited 48 patients aged 50 to 80 years at 4 study sites (Moores Comprehensive Cancer Center, University of California San Diego and San Diego Veterans Affairs Medical Center, La Jolla, CA; Roswell Park Cancer Institute, Buffalo, NY; and Waikato Hospital, Hamilton, New Zealand) with biopsy-proven noninvasive (Ta, T1, or *carcinoma in-situ*) urothelial cell carcinoma with at least a 3-year life expectancy and a willingness to be randomized to receive information about diet or to participate in dietary intervention. Institutional Review Board approval was obtained at all sites.

Exclusion criteria included psychiatric illness precluding compliance with the intervention and/or obtainment of informed consent; medical conditions which in the opinion of the treating physician made the protocol unreasonably hazardous, including infection, chronic diseases (such as diabetes mellitus, cardiac disease, ulcerative colitis, and Crohn's disease); intolerance of cruciferous vegetables; bladder cancer with distant metastases; prior cystectomy or radiotherapy; current oral anticoagulation therapy with coumadin; and unwillingness to adopt a vegetable-rich diet.

Intervention: telephone- and Skype-based dietary counseling

Patients were randomized to 6 months of telephone- or Skype-based (for New Zealand patients, $n = 1$) dietary counseling or a control condition that provided print materials only.

The principle strategy to promote dietary change in the intervention arm was a counseling protocol with individualized, one-on-one assistance tailored to each participant. The counseling protocol followed a step-wise, phased approach using social cognitive theory (10, 11). Motivational interviewing techniques were used to help participants assume and maintain responsibility for their own behavior change (12). Similar to a prior study we conducted in prostate cancer patients (13), we included 12 telephone calls over the 6-month intervention, with more frequent calls occurring during the early phase of the intervention when participants required more support in making dietary change. The protocol specified 5 calls during month one and 3 calls during month 2, followed by monthly maintenance calls during months 3 to 6.

The primary intervention behavioral goal was 7 daily vegetable servings, with at least 2 of these as cruciferous vegetables. We defined a serving size as half cup cut-up, chopped, or shredded vegetables; half cup vegetable sauce

or puree; 1 cup of raw, leafy vegetables; or three-fourth cup (6 fl. oz.) vegetable juice. Within the context of these overall targets, participants were guided to obtain an adequate intake of all essential nutrients. To enhance quality control, all counseling was conducted centrally from the Moores UCSD Cancer Center. Before beginning counseling, counselors completed an intensive 80-hour training program; moreover, counselor performance was monitored throughout the study to ensure counselor consistency and quality.

The control group was provided the Dietary Guidelines for Americans, 2005, which recommended 5 daily servings of vegetables daily and did not emphasize cruciferous vegetables (14).

Outcome variables

Diets were evaluated at baseline and again at 6-month follow-up by a series of 3 separate 24-hour dietary recalls collected interactively via telephone interview. Each set of recalls included 2 weekdays and 1 weekend day during a 2-week period to provide data on average intake over that time period. To reduce the potential for reporting bias, the assessors were blinded to the randomization allocation. Dietary data were collected and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition Coordinating Center, University of Minnesota, MI).

Plasma carotenoids are established biomarkers of vegetable intake (13, 15). Fasting blood samples were collected at baseline and at 6-month follow-up and, using high performance liquid chromatography (HPLC), analyzed for lutein, cryptoxanthin, lycopene, α -carotene, and β -carotene concentrations, which account for >90% of carotenoids in the circulation (15).

Urinary isothiocyanate (ITC) concentrations are indicators of cruciferous vegetable intake (16). Twenty-four-hour urine samples were collected at baseline and at 6-month follow-up and analyzed for cumulative urinary ITC concentrations with HPLC methodology using the cyclocondensation reaction (16–18).

All laboratory analyses were conducted in the Moores UCSD Comprehensive Cancer Center Nutrition Shared Resource Laboratory, which participates in the National Institute of Standards and Technology (NIST), U.S. Department of Commerce, Micronutrients Measurement Quality Assurance (QA) Programs, and College of American Pathologists QA Program. Blood and urine samples collected at the San Diego VA, Roswell Park Cancer Institute, and Waikato Hospital were stored at -80°C until shipment to UCSD.

Statistical analysis

The study was designed to have >80% power to detect a moderate to large 0.7 effect-size (i.e., mean difference in diet change between arms divided by the SD of change) with 50 total participants, based on a one-sided t test with $\alpha = 0.05$. The primary outcomes were changes in objective dietary biomarkers, namely α -carotene and urinary isothiocyanates, because vegetables, especially cruciferous vegetables, were a primary target of the intervention. Secondary outcomes were self-reported dietary intake of vegetables, fruits,

grains, and fat. For this pilot feasibility study, no multiple comparisons adjustment for sample size were made for the multiple outcomes.

We randomized participants in a 3:2 fashion to the dietary intervention ($N = 30$) or control arm ($N = 18$) using a block design. We randomized a larger proportion to the intervention arm to specifically and intensively investigate the feasibility of administering the behavior intervention in this pilot trial and to obtain estimates of effect-size and precision for planning a larger trial.

To test if randomization achieved comparable groups at baseline, we compared diet groups on baseline participant characteristics using two-sample tests. To examine dietary changes, we used two-sample nonparametric Wilcoxon tests to assess between-group differences from baseline to 6-month follow-up. We evaluated self-reported dietary values and biomarkers.

We conducted a sensitivity analysis to examine the robustness of results to missing data by fitting a linear mixed-effects model with dietary intake at baseline and 6 months as repeated outcome measures (19). We included a person-specific random effect to model person-person variability in intake and diet group, time (0, 6 months), and the group \times time interaction as fixed effects in the models. A significant diet \times group interaction would indicate that dietary changes differed significantly between

study arms. We transformed biomarker values to better approximate a Gaussian distribution in these models. We used a 5% significance level for all analyses.

Results

Baseline characteristics

The groups did not differ significantly in age, BMI, gender, ethnicity, education, time from diagnosis to randomization, or tumor stage (Table 1).

At 6-month follow-up, 83% of the participants completed the diet recall assessments (Table 2) and 81% (Table 3) provided blood and urine samples to complete the biomarker assays. Six (20%) participants in the intervention arm and 2 (11%) in the control arm did not complete the study (Fig. 1). The reasons for participant discontinuation were as follows: in the intervention group, 1 could not continue due to bladder cancer progression, 1 withdrew due to other medical reasons, 2 could not be contacted by phone, and 2 voluntarily withdrew for unspecified reasons; in the control group, 1 could not continue due to bladder cancer progression and 1 could not be contacted by phone.

Self-reported dietary intake

At 6-month follow-up, intervention patients reported significant increases in daily intakes of vegetable juice

Table 1. Participant characteristics at baseline, stratified by study arm, in the Dietary Intervention in Bladder Cancer Study (DIBS)

	Overall <i>N</i> = 48	Control <i>N</i> = 18	Intervention <i>N</i> = 30	<i>P</i> -value ^a
Mean age, years (SE)	66 (9)	65 (8)	66 (9)	0.93
Mean body mass index, kg/m ² (SD)	29 (7)	29 (7)	30 (8)	0.38
Gender, %				0.74
Male	75	72	77	
Female	25	28	23	
Ethnicity, %				0.53
Non-Hispanic White	88	89	87	
Hispanic	4	0	7	
Black	6	11	3	
Other	2	0	3	
Education, %				0.61
High school graduate	19	22	17	
Some college education	31	22	37	
College graduate	29	28	30	
Post-college graduate	19	28	13	
Unknown	2	0	3	
Mean time from diagnosis to randomization, years (SE)	1.5 (1.3)	1.2 (1.2)	1.7 (1.3)	0.19
Tumor stage, %				0.50
Ta	63	56	67	
T1	27	28	26.5	
Carcinoma <i>in situ</i>	10	17	6.5	

^aComparing control and intervention.

Table 2. Dietary composition comparing intervention to control at baseline and 6-month follow-up in the Dietary Intervention in Bladder Cancer Study (DIBS)

	Baseline		6-Month follow-up		P-value ^a
	Control mean (SE) N = 18	Intervention mean (SE) N = 30	Control mean (SE) N = 16	Intervention mean (SE) N = 24	
Energy (kcal/day)	1927.2 (178.3)	1946.5 (78.3) ^b	2012.6 (148.5)	1773.3 (89.8) ^b	0.007
Fat (g/day)	67.6 (7.9) ^c	80.521 (4.8) ^{c, d}	77.4 (6.7)	66.1 (4.8) ^d	0.002
Vegetable juice (servings/day)	0.07 (0.07)	0.16 (0.07) ^d	0.06 (0.06)	0.74 (0.2) ^d	0.02
Total vegetables (servings/day)	2.3 (0.2)	2.4 (0.23) ^d	2.1 (0.3)	3.9 (0.4) ^d	0.02
Cruciferous vegetables (servings/day)	0.40 (0.12)	0.49 (0.14) ^d	0.35 (0.1)	1.2 (0.2) ^d	0.07
Total fruit (servings/day)	3.74 (0.69)	3.27 (0.45)	2.46 (0.40)	2.12 (0.37)	0.97
Refined grain products (servings/day)	1.79 (0.29)	1.90 (0.15)	1.7 (0.3)	1.4 (0.3)	0.06
Whole grain products (servings/day)	1.08 (0.22)	0.86 (0.15)	1.378 (0.2)	1.35 (0.2)	0.95
Legumes, total (servings/day)	0.28 (0.21)	0.21 (0.06) ^d	0.132 (0.049)	0.47 (0.1) ^d	0.06
Legumes, soy (servings/day)	0.13 (0.08)	0.02 (0.007)	0.035 (0.023)	0.17 (0.09)	0.15
Energy from fat (%)	31.2 (2.0) ^e	37.1 (1.5) ^e	34.5 (2.3)	33.4 (1.8)	0.06

^aP value based on Wilcoxon rank sum test comparing changes in each marker between groups.

^bWithin group change P-value < 0.1.

^cBetween group difference at baseline Wilcoxon test P-value < 0.1.

^dWithin group change P-value < 0.05.

^eBetween group difference at baseline Wilcoxon test P-value < 0.05.

and total vegetables and lower daily intakes of total energy (kcal/d) and fat (g/d) compared to control patients. Although not significant at the 5% level, daily intakes of cruciferous vegetables and legumes increased and energy from fat decreased in the intervention compared to the control groups (Table 2).

Dietary biomarkers

At 6-month follow-up, intervention patients showed significant increases from baseline in plasma α -carotene concentrations compared to controls. Although intervention patients also had increases from baseline in plasma lycopene, β -carotene, and total carotenoids compared to

Table 3. Dietary biomarkers comparing intervention to control at baseline and 6-month follow-up in the Dietary Intervention in Bladder Cancer Study (DIBS)

	Baseline		6-Month follow-up		P-value ^a
	Control mean (SE) N = 18	Intervention mean (SE) N = 30	Control mean (SE) N = 15	Intervention mean (SE) N = 24	
Lutein plus zeaxanthin ($\mu\text{mol/L}$) ^b	0.38 (0.04) ^c	0.33 (0.07) ^c	0.37 (0.03)	0.32 (0.05)	0.97
Cryptoxanthin ($\mu\text{mol/L}$) ^b	0.19 (0.04)	0.19 (0.06) ^d	0.18 (0.04)	0.13 (0.03) ^d	0.42
Lycopene ($\mu\text{mol/L}$) ^b	0.78 (0.06)	0.65 (0.06)	0.76 (0.11)	0.68 (0.08)	0.38
Alpha-carotene ($\mu\text{mol/L}$) ^b	0.20 (0.03) ^e	0.14 (0.04) ^{e, f}	0.17 (0.03)	0.16 (0.03) ^f	0.03
Beta-carotene ($\mu\text{mol/L}$) ^b	0.62 (0.09) ^e	0.47 (0.09) ^e	0.69 (0.16)	0.55 (0.08)	0.40
Total carotenoids ($\mu\text{mol/L}$) ^b	2.2 (0.18) ^e	1.70 (0.19) ^e	2.2 (0.29)	1.80 (0.20)	0.60
Isothiocyanate ($\mu\text{mol/L}$) ^g	95.5 (42.9)	40.0 (14.4)	56.9 (23.0)	59.9 (14.8)	0.32

^aP-value based on Wilcoxon rank sum test comparing changes in each marker between groups.

^bPlasma.

^cBetween group difference at baseline Wilcoxon test P-value < 0.1.

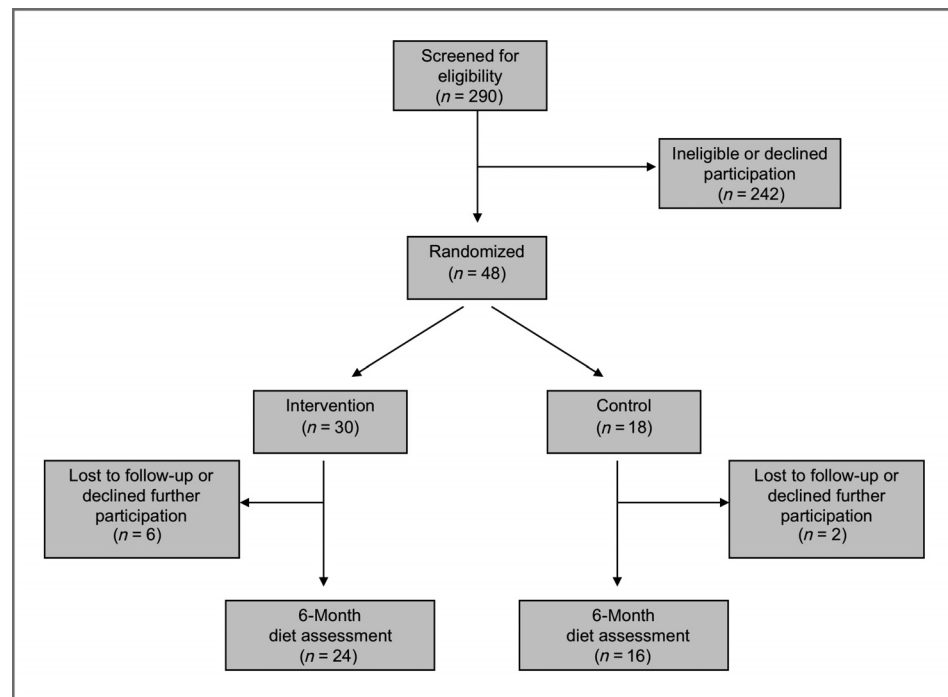
^dWithin group change P-value < 0.1.

^eBetween group difference at baseline Wilcoxon test P-value < 0.05.

^fWithin group change P-value < 0.05.

^gUrine.

Figure 1. Composition of the study population in the Dietary Intervention in Bladder Cancer Study (DIBS).



controls, these differences did not attain significance (Table 3).

Self-reported cruciferous vegetable intake correlated significantly with 24-hour urinary ITC concentrations at both baseline (Spearman $r = 0.63$, $P = 0.005$) and 6-month follow-up (Spearman $r = 0.45$, $P = 0.03$). Although urinary ITC concentrations increased in the intervention arm and decreased in the control arm, these changes did not attain significance among the patients for whom 6-month comparison data were available (Table 3). Sensitivity analysis using mixed model yielded concordant results (Appendix).

Discussion

In this randomized pilot trial in patients with noninvasive bladder cancer, our novel dietary counseling intervention significantly increased vegetable intake and plasma α -carotene concentrations, significantly decreased fat and total energy intake, and marginally significantly increased cruciferous vegetable intake. In the intervention group, self-reported intake of cruciferous vegetables more than doubled ($P < 0.05$ for within group change and $P = 0.07$ for between group change; Table 2) and for total vegetable intake increased by more than 60% ($P < 0.05$ for within group change and $P = 0.02$ for between group change; Table 2). This trial is the first clinical study of a dietary intervention for bladder cancer and shows the feasibility of implementing therapeutic, chemopreventive lifestyle modifications in patients with bladder cancer.

The aim of this pilot study was to develop a feasible clinical intervention that produces changes in the diets of bladder cancer patients consistent with the putative benefits of prior epidemiological and preclinical data. Although the

majority of prior evidence supports a role for dietary modification in primary prevention (6, 8, 9), at least one study observed a survival benefit for higher crucifer intake among bladder cancer survivors (7). Moreover, given the relatively high incidence of recurrence and progression, a compelling argument can be made in favor of the clinical relevance of tertiary prevention applications. Approximately 75% to 85% of patients with bladder cancer initially present with noninvasive disease; of these, 50% to 90% will recur or progress to invasive disease within 3 to 5 years despite aggressive local therapy (20, 21).

An additional finding was that self-reported cruciferous vegetable intake correlated with 24-hour urinary ITC concentrations. This finding is consistent with prior feeding studies in cohorts of hospitalized and nonhospitalized study participants (16, 22–26) and confirms that urinary ITC concentration is a robust biomarker for cruciferous vegetable intake in the setting of an outpatient clinical trial for cancer.

Unlike the increases in reported total and cruciferous vegetable intakes, changes in total carotenoids, lycopene, β -carotene and in the urinary ITC concentrations did not attain significance, most likely because of the relatively small sample sizes (Fig. 1). Although the changes were nonsignificant, total carotenoid and isothiocyanate concentrations in the intervention group increased whereas those in the control group decreased or remained stable, consistent with the intervention emphasis on cruciferous vegetables. Larger sample sizes would be needed to definitively show biomarker changes.

In addition, although objective biomarkers are useful metrics, they should not necessarily be regarded as a gold

standard for measuring relevant intakes of nutrients in clinical trials, nor should they substitute for diet recall data. Individual variations in variables including, but not limited to, recent macronutrient intake (especially fat), BMI, and ethnicity may potentially influence serum and urinary concentrations of these biomarkers and introduce systematic biases (27). Biomarkers and dietary recall measures should thus be used as complementary metrics.

We believe these results will inform the design of a phase III trial of dietary modification to prevent recurrence and progression among patients with noninvasive bladder cancer. Specific data we will consider for trial design include the following: first, the carotenoid and ITC biomarker results, which suggest that power calculations for a phase III trial will require consideration of a larger sample size than originally anticipated; second, the adherence data, which suggest an anticipated dropout rate of up to 20% (Fig. 1); and, finally, the observation that 24-hour urinary ITC concentrations correlated with self-reported cruciferous vegetable intake, which potentially allows for greater reliance on patient self report, which would free patients of burdensome 24-hour urine collections and possibly increase adherence to follow-up.

Our intervention is practicable, demands few resource commitments on the part of the patient, and is low cost to implement among relatively large and geographically diverse study populations. The intervention uses straightforward, rational strategies adopted from social cognitive theory (10, 11) using the techniques of motivational interviewing (12). Similar interventions have produced marked changes in the diet and increased plasma carotenoids in both breast cancer (28, 29) and prostate cancer (13, 30) patients.

Notably, because obesity and poor diet disproportionately affect African Americans and Hispanics (31), this intervention may be particularly relevant for addressing health care disparities for bladder cancer among underserved minorities. Compared to non-Hispanic Whites, African Americans with bladder cancer experience diminished cancer-specific and overall survival, are more likely to present with higher grade and higher stage disease, and have increased risks of adverse outcomes after cystectomy, including prolonged length of stay and death (32). Bladder cancer incidence and mortality are also higher among Hispanics compared to non-Hispanic Whites (33, 34).

Carotenoids, which occur in high concentrations in tomatoes, carrots, and other deeply pigmented vegetables, are putative anticarcinogenic agents. Prior studies have observed strong associations of higher plasma carotenoid concentrations with decreased risks of incident bladder cancer. In one analysis comparing the highest quartiles to the lowest, plasma total carotenoids (RR = 0.64; 95% CI, 0.44–0.93; $P_{\text{trend}} = 0.04$) and β -carotene (RR = 0.51; 95% CI, 0.30–0.88; $P_{\text{trend}} = 0.02$) were inversely associated with aggressive and plasma lutein (RR = 0.56; 95% CI, 0.32–0.98; $P_{\text{trend}} = 0.05$) with nonaggressive cancers, respectively (35). In another study, higher concentrations of α -carotene (RR = 0.22; 95% CI, 0.05–0.92), lutein (RR = 0.42; 95% CI,

0.18–1.00), zeaxanthin (RR = 0.16; 95% CI, 0.02–1.06), lycopene (RR = 0.94; 95% CI, 0.89–0.99), and β -cryptoxanthin (RR = 0.90; 95% CI, 0.81–1.00) were associated with decreased risks of incident disease (36).

Cruciferous vegetables—such as broccoli, kale, and radishes—are rich in ITCs. ITCs are potent inducers of phase II cytoprotective enzymes, including glutathione S-transferase (GST) and NAD(P)H:quinolone oxidoreductase 1 (NQO1). Cruciferous vegetables are believed to exert anticarcinogenic effects through induction of these enzymes. Several studies have observed an increased risk of urothelial carcinoma in individuals with GST and NQO1 genotypes associated with null or suboptimal phenotypes (37–40). Similarly, a case-control study reported that increased consumption of ITCs was associated with a 29% decreased risk of incident bladder cancer (41), and ingestion of ITC-rich broccoli sprout extract significantly inhibited bladder carcinogenesis in a rat model (42).

Strengths of this pilot study include its novel yet practical therapeutic strategy for bladder cancer primary or tertiary chemoprevention, randomized trial design that produced balanced study arms, 85% participant retention rate, and comprehensive dietary assessments. One potential limitation was the limited sample size, which could have reduced the study power to detect significant differences in most of the biomarkers. Another potential limitation is that it is unclear whether the observed changes in diet and plasma α -carotene will persist beyond 6 months. However, a prior study of breast cancer suggests that these changes could continue for at least 4 years after the initial application of the intervention (28). Finally, it is possible that recall bias occurred in that the intervention participants may have differentially reported consuming the recommended foods to please the interviewer. However, a prior analysis of diet change in breast cancer patients concluded that, although there is a potential increase in systematic error for diet assessment in an intervention group, the validity (i.e., correlation with "true" intake) of self-report is significantly higher during follow-up for intervention versus nonintervention participants (43). Thus, although the potential for error existed among self-reported diet in the intervention group, so did the potential for increased validity.

Conclusions

In patients with noninvasive bladder cancer, our novel intervention induced dietary changes associated with protective effects against bladder cancer. These data show the feasibility of implementing therapeutic, chemopreventive dietary modifications in bladder cancer patients and support the performance of phase III clinical trials focused on preventing incident, recurrent, and progressive disease.

Disclosure of Potential Conflicts of Interest

K. Guru is employed (other than primary affiliation; e.g., consulting) as a board member in Simulated Surgical Systems. K. Guru is also a consultant/advisory board in Simulated Surgical Systems. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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